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# World Heart Congress

THE LARGEST and most important congress on heart disease ever held in America will convene Sept. 12 through 17, 1954, in Washington, D. C., when the Second World Congress of Cardiology will meet in association with the Twenty-seventh Annual Scientific Sessions of the American Heart Association. This is the first time that the meeting of the international heart organization has been held in the United States.

Opening ceremonies will take place in Constitution Hall on Sunday, September 12. It is hoped that President Eisenhower will render the opening welcome to the foreign and American physicians. An attendance of 3,000 is anticipated. During the next five days, scientific sessions and exhibits will be held at the National Guard Armory in southwest Washington. Because of the international character of the meeting all panel sessions will be presented simultaneously in French, Spanish and English, over IBM earphones as in the United Nations, by U. S. State Department translators.

The heart congress should be one of the most important medical meetings held in our time. Diseases of the heart and great blood vessels rank first as causes of death in the United States and many other nations, and a discussion of this subject will attract leading medical authorities from far and wide throughout the world. The breadth of the Congress is typified by the topics of the major panel discussions on international cardiovascular epidemiology, congenital cardiovascular defects, rheumatic fever and rheumatic heart disease, cardiovascular physiology and cardiac surgery.

Special visits for the physicians of the Congress have been arranged to the National Heart Institute of the United States Public Health Service, Bethesda, Md.; to the medical schools and hospitals of Washington; to the Walter Reed Army Medical Center and to the great Army Medical Library, the world's largest in the field of medical literature.

Social entertainment of the members of the Congress will add much to the enjoyment of the visitors to Washington. Evening programs will include a visit to the renowned National Gallery of Art, which will be opened especially for the congressionists, a banquet, a concert, and entertainment at private homes for members from abroad. Sightseeing tours of Washington and its environs are also being planned.

The fees for membership in the Congress include admission to scientific sessions and scientific tours in and about Washington and to the evening social events. They defray only a fraction of the cost of the Congress which is being supported also by the American Heart Association, the National Heart Institute, the commercial exhibitors, and various private individuals and agencies.

Following the Congress, tours to other medical centers in the United States and Canada are being arranged, lasting from ten days to several weeks. Details of all these plans can be obtained by writing to Dr. L. Whittington Gorham, Secretary-General, World Heart Congress, 44 East 23rd Street, New York, N. Y.

This Congress will help to establish a baseline for the future in our attack on cardiovascular disease. The next Congress four years from now will be held in the old world where the International Society of Cardiology had its birth at the First Congress in Paris in 1950, and in eight years the Congress will return to the new world. One may hope that this Second World Congress of Cardiology will stimulate the youth of today to hold high the torch to light the way to the international research and medical cooperation of the years to come.

PAUL D. WHITE
*Chairman, Organizational Committee*

# Treatment of Stokes-Adams Disease by External Electric Stimulation of the Heart

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An external cardiac pacemaker was developed and was used to stimulate the heart electrically in a series of patients with recent Stokes-Adams syncope. It resuscitated patients from attacks due to ventricular standstill; it maintained an adequate circulation during persistent ventricular standstill; and it prevented the recurrence of irregular ventricular tachycardia. Several patients have now survived for many months without recurrent syncope. Such long survivals suggest that the periods of cardiac disturbance which cause syncope may subside if the patient is kept alive during the crucial period.

THE syncopal attacks of Stokes-Adams disease are unpredictable and often present desperate therapeutic problems. These episodes of circulatory arrest due to ventricular standstill, tachycardia or fibrillation may become very frequent and severe. A fatal attack is always imminent. Furthermore, the available therapy with drugs and cardiac puncture is dangerous and may be ineffective in resuscitating patients from individual attacks or in maintaining adequate ventricular rhythms.

We have developed a new therapeutic approach to this serious problem. This consists of electric stimulation of the heart by means of an externally-applied cardiac pacemaker which terminates ventricular standstill and maintains regular externally-paced ventricular beats until an adequate, spontaneous ventricular rhythm reappears. After experimental studies in animals established the efficacy and safety of this procedure, it was used in the treatment of patients with recent Stokes-Adams attacks.

Presented in part before the New England Cardiovascular Society, Feb. 9, 1953, and before the Scientific Sessions of the 26th Annual Meeting of the American Heart Association, Atlantic City, N. J., April 10, 1953, and the American Society for Clinical Investigation, May 4, 1953.

From the Medical Research Department of the Yamins Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

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## APPARATUS

The cardiac pacemaker* is a modification of existing physiologic stimulators. It produces monophasic, rounded electric impulses with an average duration of 2 to 3 milliseconds and with the entire wave form lying above the baseline. A variety of other wave forms (monophasic and biphasic spike, monophasic and biphasic rectilinear, and sinusoidal) were found to be less effective. The apparatus is light, portable and simple to use, with two controls permitting variation of frequency from 30 to 180 stimuli per minute and of amplitude from 0 to 150 volts. The low internal impedance of the instrument (approximately 50 ohms) permits adequate power output even across low body resistances. In the design of the instrument, the line voltage is carefully isolated to prevent its accidental transfer to the output circuit.

The pacemaker is attached to the patient by two output wires connected to 3 cm. circular chest electrodes. The electrodes may be placed in any positions on the chest that provide current flow across the heart. For convenience, the negative electrode is placed at the point of maximum cardiac impulse, and the positive electrode symmetrically, on the right anterior chest. Good electric contact is made with electrode paste and the electrodes are held in place by a rubber strap encircling the chest.

Satisfactory recordings of the electric stimuli from the cardiac pacemaker and of the activity of the heart can be obtained electrocardiographically. The electric stimuli often displace the base line markedly and distort the electrocardiogram or mask it completely. However, recording difficulties are avoided with late model electrocardiographs that do not have

* The Cardiac Pacemaker is manufactured by the Electrodyne Company, Norwood, Mass.

condensers in the input circuit. The patient, the pacemaker and the electrocardiograph must have a common ground. This is conveniently provided by wires between the electrocardiograph and the pacemaker, and between the pacemaker and an external ground. The patient is grounded by the negative output wire from the pacemaker. It is preferable not to use the conventional ground wire from the electrocardiograph to the right leg. The most satisfactory recordings are obtained with lead $aV_F$ at half-normal standardization in order to diminish the amplitude of the deflections produced by the stimuli. Occasionally, a fuse in the patient circuit of the electrocardiograph may be blown and should be replaced.

In every patient the threshold of effective stimulation is first determined. With the frequency of stimulation set between 60 and 90 per minute, the amplitude control is increased from 0 until cardiac responses are obtained. Thereafter, effective cardiac stimulation is maintained by amplitudes slightly above the threshold level. The current and voltage of effective stimuli, measured with an oscilloscope at the chest electrodes, ranged from 75 to 150 milliamperes and from 45 to 100 volts in our patients.

## Case Reports

The cardiac pacemaker has been used in 14 patients with recent Stokes-Adams attacks. Eleven patients were treated with short or prolonged periods of stimulation for resuscitation from syncope or for maintenance of an adequate ventricular rhythm. In two additional patients trial stimulation produced effective beats, but treatment did not become necessary. In the fourteenth patient the efficacy of stimulation was not determined.

*Case 1.** E. B. (B.I.H. No. M39623), a 63 year old man, had complete heart block and occasional syncopal attacks for two years. He entered the Beth Israel Hospital because of increasingly frequent episodes of syncope, culminating in one attack lasting 20 minutes.

On admission, external electric stimulation was found to be effective in producing cardiac responses during slow idioventricular rhythm (fig. 1*a*). Shortly after this trial, ventricular standstill and syncope occurred. The external pacemaker was started immediately and the patient revived at once. Each stimulus produced a ventricular response in the electrocardiogram and a pulse beat with a pressure of 130/80. The dependence of the electrocardiographic response, the peripheral pulse and consciousness upon the electric stimuli was repeatedly demonstrated by varying the rate of stimulation. Whenever the external pacemaker was stopped for short test intervals, syncope due to ventricular standstill recurred (fig. 1*b*). External stimulation was necessary for the next 90 hours to maintain an effective circulation. Initially the patient was very restless and complained bitterly of the electric shocks and the associated twitches of the pectoral muscles. This discomfort was relieved by meperidine hydrochloride (Demerol); with continued stimulation it became much less severe.

On the third day, stimulation was inadvertently interrupted for two and one-half minutes. A prolonged Stokes-Adams attack occurred, manifest by circulatory and respiratory arrest, convulsions and syncope. Resumption of external stimulation revived the patient immediately, but it was more than 18 hours before complete mental clearing occurred.

Various medications were given in an effort to arouse a spontaneous, sustained idioventricular rhythm. Sustained idioventricular beats finally appeared when the rate of intravenous administration of epinephrine was raised to 8 micrograms per minute. When these beats persisted at an effective rate (fig. 1*c*), both the external stimulation and the administration of epinephrine were stopped.

The slow spontaneous rhythm persisted for the next nine days. Occasionally the pacemaker was tested and was found to be effective. During this time, there were no signs of circulatory or cerebral damage and the patient felt well.

Suddenly, on the thirteenth hospital day, the patient had another Stokes-Adams attack; respiration stopped, heart sounds and motor activity disappeared, and the patient seemed dead. Because of a lapse in readiness, there was a delay of five minutes before stimuli were reapplied. Resumption of external stimulation resulted in immediate ventricular responses and return of peripheral circulation. Thereafter, the heart rate was maintained by the pacemaker, but coma, restlessness, coarse tremor and high fever indicated progressive cerebral damage. Repeated attempts to arouse spontaneous ventricular beats with intravenous epinephrine and norepinephrine failed. After 108 hours of stimulation, the blood pressure dropped despite increasing rates of norepinephrine infusion; respirations and ventricular responses to the stimuli ceased, and the patient died.

*Case 2.* I. L. (B.I.H. No. M37752), an 80 year old woman with complete heart block for 30 years, was admitted to the Beth Israel Hospital because of recent, repeated syncopal attacks. These were due to ventricular standstill, rapid ventricular tachycardia or both (fig. 2*a*).

During complete heart block, external electric stimulation produced synchronous electrocardiographic responses and pulse beats. Accordingly, stimulation was applied, at first intermittently to

* For simplicity of presentation, these cases are not reported in chronologic order or in the sequence followed in the discussion.

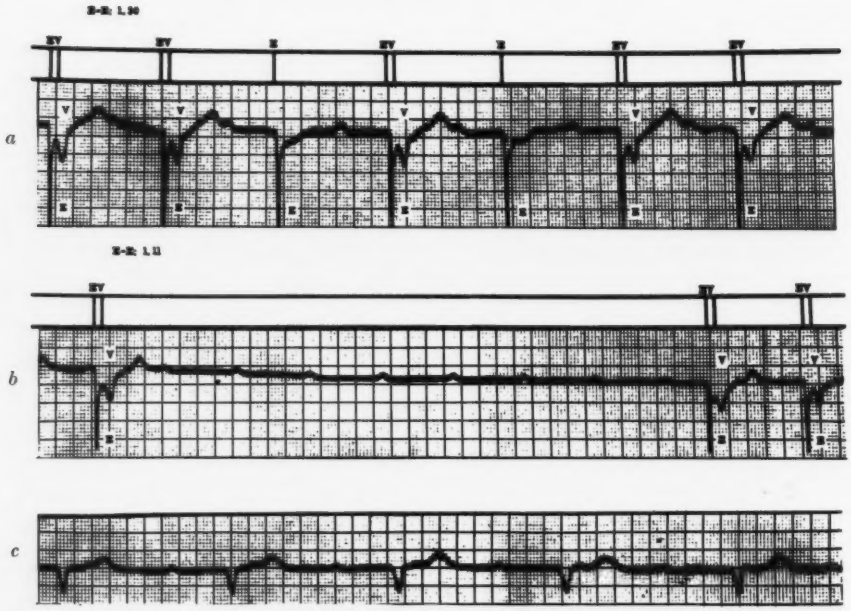

FIG. 1. Case 1. Lead $aV_F$; standardization half normal (1 mv. equals 5 mm.). (*a*) *External electric stimulation during slow idioventricular rhythm:* In all figures, *E* indicates an electric stimulus and *V* indicates a ventricular response. These stimuli were of threshold intensity and, accordingly, were occasionally ineffective: the third and fifth stimuli were not followed by ventricular responses. The independent atrial rhythm (cycle length 0.64 second) was uninterrupted. (*b*) *Temporary interruption of electric stimulation during ventricular standstill:* During a test period of 6.9 seconds no stimuli were applied. No spontaneous ventricular contractions occurred during this interval and the patient lost consciousness. The independent atrial rhythm continued. Resumption of stimuli (*E*) immediately gave ventricular responses (*V*) and the patient revived at once. (*c*) *Control electrocardiogram:* Complete heart block: atrial cycle 0.92 second; ventricular cycle 1.92 second.

resuscitate the patient from syncope, and then almost continuously for 24 hours to prevent syncope. The electric stimuli produced moderate contractions of the thoracic muscles, particularly the left pectorals. Initially these movements startled the patient and the stimuli were somewhat painful. After moderate sedation with meperidine hydrochloride and continued stimulation, the patient tolerated the procedure with little discomfort.

The efficacy of external stimulation in preventing

FIG. 2. Case 2. Lead $aV_F$; standardization half normal (1 mv. equals 5 mm.). (*a*) *Stokes-Adams attack due to rapid ventricular tachycardia and ventricular standstill:* Paroxysm of rapid ventricular tachycardia (rate approximately 230 per minute) followed by ventricular standstill for 3.6 seconds before resumption of idioventricular rhythm. Syncope occurred during the tachycardia and standstill. (*b*) *Effective stimulation at varying rates:* Each stimulus (*E*) produced a ventricular response (*V*). Each electrocardiographic ventricular response depended upon an electric stimulus as shown by the constant relationship at widely varying rates of stimulation. (*c*) *Ventricular standstill during temporary interruption of stimulation:* During a test period of 6.6 seconds no stimuli were applied. No spontaneous ventricular contractions occurred during this interval and the patient lost consciousness. The independent auricular rhythm continued. Resumption of stimuli immediately gave ventricular responses and the patient revived at once. (*d*) *Rapid ventricular tachycardia during temporary interruption of stimulation:* The paroxysm of ventricular tachycardia lasted 5.4 seconds, produced syncope, and terminated spontaneously. After a pause of one second spontaneous multifocal ventricular beats occurred. (*e*) *Ineffective stimulation during paroxysm of rapid ventricular tachycardia:* This paroxysm occurred shortly after the one shown in figure 2d during the same test period. The two paroxysms are almost identical. Stimuli (*E*) applied during the second half of this paroxysm produced no cardiac effect. After the paroxysm had stopped, apparently spontaneously, stimuli evoked ventricular responses (*V*).

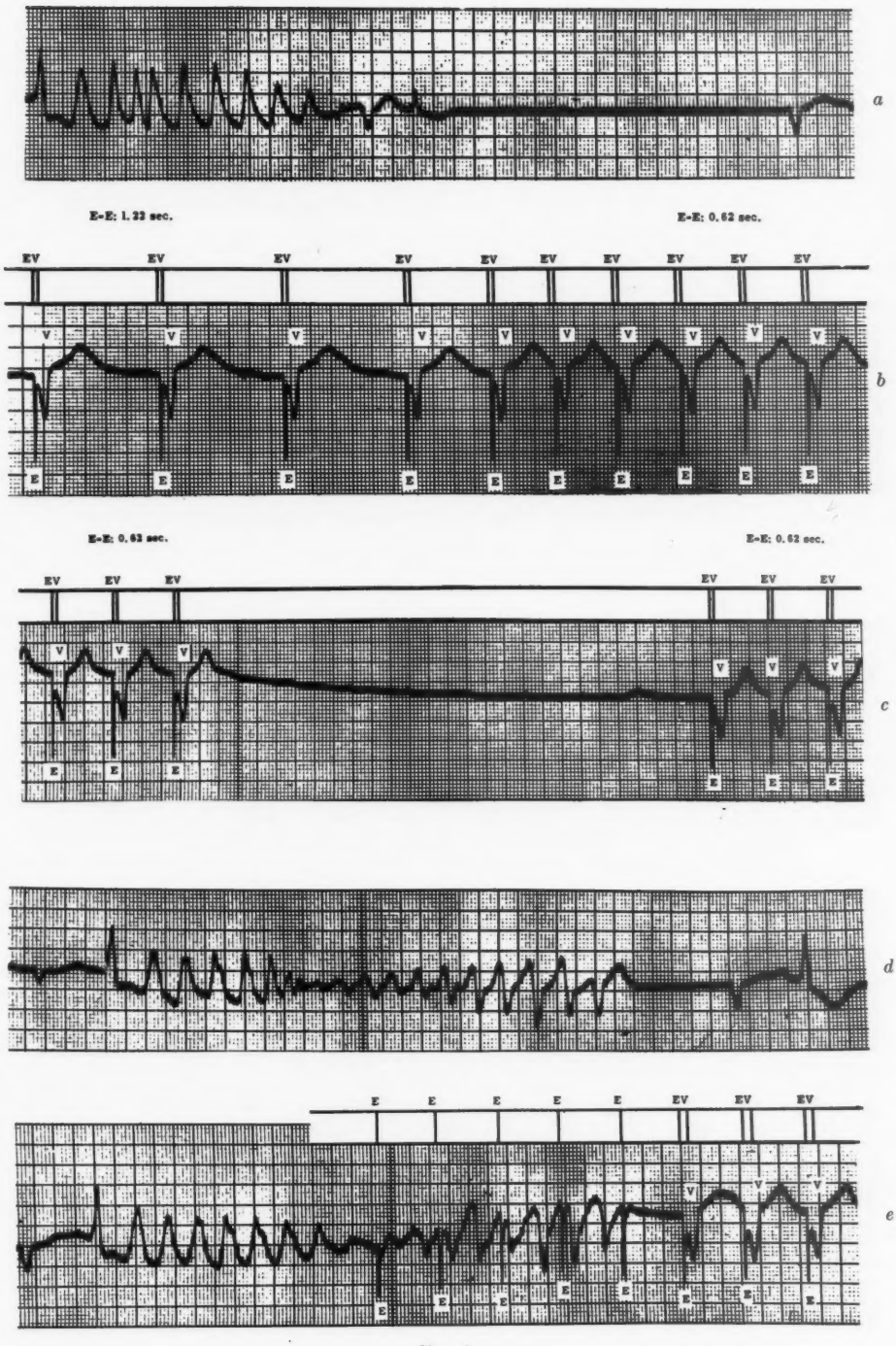


FIG. 2.

Stokes-Adams attacks was repeatedly demonstrated during the 24 hour period. During stimulation syncope never occurred. The electric stimuli produced uninterrupted, effective ventricular beats at rates which were varied from 50 to 100 per minute (fig. 2*b*). The spontaneous, irregular ventricular activity did not break into the slower, externally-paced rhythm. When stimulation was interrupted for short test periods, syncope occurred due to the absence of spontaneous ventricular contractions (fig. 2*c*) or to rapid ventricular tachycardia (fig. 2*d*). Although stimulation was effective in preventing rapid ventricular activity, it failed to terminate such paroxysms (fig. 2*e*).

After 24 hours of external stimulation, the periods of ventricular standstill and rapid ventricular activity gradually disappeared. The external pacemaker was then stopped completely and a slow, idioventricular rhythm continued. The patient has now survived 12 months without further syncope.

*Case 3.* L. W. (B.C.H. No. 1481070), a 71 year old woman with occasional Stokes-Adams attacks for two years, was admitted to the Boston City Hospital because of their increasing frequency. On admission, electrocardiograms showed complete heart block and short paroxysms of rapid, irregular ventricular activity. Soon thereafter, the patient had two major syncopal attacks lasting four minutes and one minute. They were due to prolonged ventricular fibrillation followed by short periods of ventricular standstill.

Throughout her hospitalization, atrioventricular conduction changed frequently, ranging from normal P-R intervals with regular sinus rhythm to complete heart block. The external cardiac pacemaker produced electrocardiographic ventricular

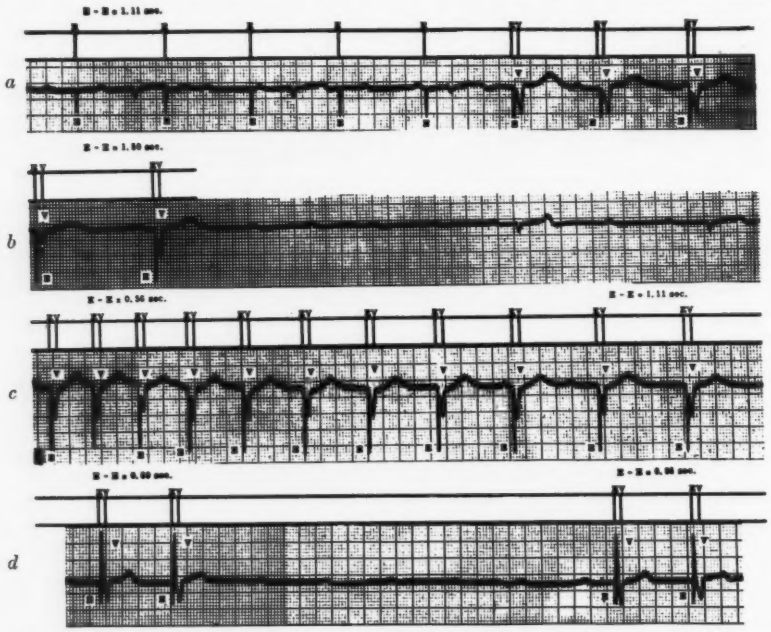


FIG. 3. Case 3. Lead $aV_F$; standardization half-normal (1 mv. equals 5 mm.). (*a*) *Interruption of idio-ventricular rhythm by faster externally-paced beats:* The intensity of the electric stimuli (*E*) was progressively increased until ventricular responses (*V*) were produced. Three spontaneous idioventricular complexes (cycle length 2.04 seconds) are seen during ineffective stimulation; during effective stimulation at a faster rate (cycle length 1.11 seconds) they are suppressed. (*b*) *Resumption of idioventricular rhythm following external stimulation:* When stimulation was stopped, the spontaneous ventricular pacemaker reappeared after a pause of 4.64 seconds and regained its previous rate within three beats. (*c*) *Effective stimulation at varying rates:* Each stimulus (*E*) produced a ventricular response (*V*). Each electrocardiographic ventricular response depended upon an electric stimulus as shown by the constant relationship at widely varying rates of stimulation. (*d*) *Ventricular standstill during temporary interruption of stimulation:* During a test period of 5.5 seconds no stimuli were applied. No spontaneous ventricular contractions occurred during this interval and the patient lost consciousness. The independent atrial rhythm continued. Resumption of stimuli immediately gave ventricular responses and the patient revived at once.

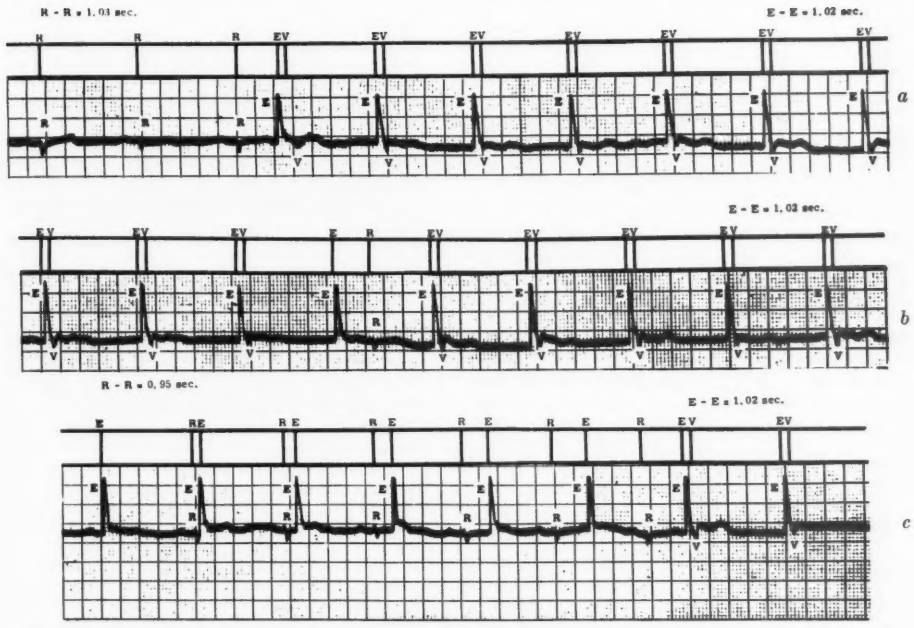


FIG. 4. Case 3. Lead $aV_F$; standardization half-normal (1 mv. equals 5 mm.) *External electric stimulation during normal sinus rhythm.* The three strips were taken during a period of continuous stimulation. (*a*) After three sinoatrial beats (*R*) stimulation at a similar rate was started and immediately produced ventricular responses (*V*). (*b*) During the externally-paced rhythm at threshold voltage the fourth stimulus was ineffective and was followed by an escape beat (*R*) from the sinoatrial pacemaker. (*c*) After 25 seconds of stimulation at the same rate ($E-E = 1.02$ seconds), the sinoatrial rate increased ($R-R$ shortened from 1.03 to 0.95 seconds) and competition is observed between the sinoatrial and external pacemakers. The normal pacemaker maintained control of the ventricles for seven beats (*R*). The first sinoatrial beat is partially masked by a stimulus. During this sinoatrial rhythm the electric stimuli were ineffective because they fell in the refractory phase of the ventricles. As soon as a stimulus (the seventh *E*) arrived during the responsive phase of the ventricles it was effective and the external pacemaker resumed control of the heart.

responses and synchronous pulse beats during complete heart block (fig. 3), partial heart block and normal sinus rhythm (fig. 4).

Frequent and severe syncopal attacks occurred during complete heart block. Although rapid irregular ventricular activity occasionally recurred, the predominant mechanism of syncope was ventricular standstill. On eight occasions in two months prolonged stimulation was necessary for periods ranging from 6 to 48 hours to maintain an adequate circulation until a spontaneous sustained pacemaker reappeared. The intervals of stable rhythms between periods of stimulation varied from 2 hours to 19 days. Heavy sedation with narcotics, barbiturates and paraldehyde was required to control severe discomfort produced by the stimulation.

The patient's clinical course was complicated by severe, transient pulmonary infections. She has now survived for seven months since the initial resuscitation by the cardiac pacemaker and she has had no syncope during the past five months. Her present condition in a convalescent hospital is satisfactory, and she shows no deleterious effects on her mental or cardiac function as a result of either the prolonged stimulation or syncope.

*Case 4.* R. A.* (B.I.H. No. M34234), a 65 year old man with complete heart block, was admitted to the Beth Israel Hospital because of congestive heart failure and angina pectoris. Repeated Stokes-Adams attacks due to ventricular standstill and rapid irregular ventricular activity occurred in the hospital.

External electric stimulation was effective and stopped syncopal attacks. For five days, because of recurrent ventricular standstill, repeated electric stimulation was necessary until an adequate sustained idioventricular rhythm reappeared.

The patient lived for 10 months, free of syncope and without increase in his cardiac disability. He then died suddenly.

*Case 5.* D. S.* (B.I.H. No. M33443), a 75 year old man with complete heart block, was admitted to the Beth Israel Hospital because of repeated Stokes-Adams attacks due to ventricular standstill and rapid irregular ventricular tachycardia. Over a four hour period 34 cardiac injections of epinephrine were given.

External electric stimulation was effective and stopped syncopal attacks during a 25 minute period. Stimulation then became ineffective and the patient died because of cardiac tamponade which resulted from the cardiac punctures.

*Case 6.* P. G. (B.C.H. No. 1485391), a 78 year old man, was admitted to the Boston City Hospital because of frequent dizzy spells for two weeks. Electrocardiograms showed varying degrees of partial atrioventricular block, and then complete block with idioventricular rates as slow as 16 beats per minute. Initially he had numerous dizzy spells, then he became unconscious and never fully recovered.

External electric stimulation was effective: an adequate circulation was maintained with a blood pressure of 118/60. Continued stimulation was necessary for 36 hours because ventricular standstill was observed whenever stimulation was interrupted. An adequate idioventricular rhythm reappeared following the intravenous administration of epinephrine at a rate of 4 micrograms per minute and stimulation was then stopped.

Ten hours later, however, the ventricular rate slowed markedly and shock supervened. At this time, stimulation again produced electrocardiographic ventricular complexes, but there were no associated pulse beats. Finally, the electrocardiographic ventricular responses to stimulation also failed and the patient died.

*Case 7.* B. S. (P.B.B.H. No. C5205), an 81 year old woman, entered the Peter Bent Brigham Hospital because of three syncopal attacks. After admission, cardiac arrest, requiring cardiac puncture in order to restore the beat and resuscitate the patient, occurred approximately 30 times. Electrocardiograms showed regular sinus rhythm with normal P-R intervals, 2:1 atrioventricular block and variable ectopic supraventricular pacemakers. Paroxysms of rapid, irregular ventricular tachycardia followed by ventricular standstill were observed to cause syncope.

Accordingly, on the second hospital day, external electric stimulation was applied. The stimuli produced synchronous ventricular complexes and pulse beats with the patient's usual pressure of 120/80. The electric stimuli produced only slight pectoral twitch and little discomfort.

Immediately upon effective stimulation the syncopal attacks stopped. Stimulation was discontinued after five hours and syncope did not recur until 19 hours later. The attacks again ceased when effective stimuli were reapplied. Stimulation was continued for eight hours and the patient then had no further attacks for eight days.

Finally on the tenth hospital day the patient had another Stokes-Adams attack and expired. Necropsy showed a small bloody pericardial effusion and pericarditis due to the cardiac punctures.

*Case 8.* A. R. (B.I.H. No. M42953), a 76 year old woman, entered the Beth Israel Hospital because of chronic lymphatic leukemia and congestive heart failure. She was known to have had complete heart block and occasional syncopal attacks for one year.

On the sixth hospital day, following a prolonged Stokes-Adams attack, external electric stimulation was applied during slow idioventricular rhythm. Electrocardiographic ventricular responses and pulse beats were observed synchronous with the electric stimuli. The patient was disturbed by the muscle contractions and the pain associated with stimulation. Electric stimulation was reapplied three times on this day for recurrent Stokes-Adams attacks due to rapid ventricular tachycardia. Although stimulation was ineffective during the paroxysms of tachycardia, it became effective immediately when they stopped.

Two days later, another prolonged Stokes-Adams attack occurred and consciousness never completely returned. During the next hour, multifocal ventricular beats and paroxysms of irregular ventricular tachycardia predominated. Periods of ventricular standstill which frequently followed ventricular tachycardia were repeatedly terminated by external stimulation. Electric stimulation was applied almost continuously for the next 10 hours. At first an effective ventricular rhythm was maintained with only infrequent interruptions by spontaneous ventricular beats. Near the end of this period of stimulation, however, spontaneous irregular ventricular activity increased until persistent ventricular tachycardia supervened and stimulation became ineffective. The blood pressure then fell, the temperature rose to 105.7 F. and the patient died.

Necropsy showed no evidence of cardiac damage attributable to electric stimulation.

*Case 9.* A. S. (B.C.H. No. 1481716), an 82 year old woman with a past history of complete heart block and Stokes-Adams attacks, was readmitted to the Boston City Hospital because of recurrent syncope. Shortly thereafter she became unconscious. Repeated convulsive seizures were observed due to ventricular fibrillation followed by ventricular standstill. In one episode, recorded electrocardiographically, ventricular fibrillation lasted for three minutes.

External electrical stimulation was applied effectively for 20 hours. Although the patient improved and became somewhat responsive, convulsive

* Cases 4 and 5, the first two patients treated, have been reported in detail.[1]

seizures continued. Spontaneous, multifocal ventricular beats frequently broke through the externally-paced rhythm. Finally, during a test interruption of effective stimulation, a convulsion occurred, the stimuli were then ineffective and the patient died.

*Case 10.* A. L. (B.I.H. No. M42806), a 72 year old woman, entered the Beth Israel Hospital because of increasing cardiac pain and congestive failure. Although her rhythm had been normal and digitalis had not been given, after hospitalization she was found to have complete heart block with multifocal ectopic ventricular beats and paroxysms of irregular ventricular tachycardia. Two severe Stokes-Adams episodes occurred which were treated with intracardiac injections of hydroxyamphetamine hydrobromide (Paredrine).

External electric stimulation was effective during slow idioventricular rhythm. However, the patient found it too painful to permit continuous application. Over a six-day period, external stimulation was applied during eight syncopal attacks, and consciousness returned promptly on each occasion. Satisfactory electrocardiographic observations of the mechanisms of these attacks were not obtained.

Electric stimulation was ineffective during the last 50 seconds of another syncopal attack which was due to rapid irregular ventricular tachycardia. As soon as the tachycardia stopped, apparently spontaneously, the stimuli immediately evoked ventricular responses and pulse beats. Finally, the patient died during a Stokes-Adams attack in which electric stimulation, though applied promptly, was ineffective.

Necropsy showed no evidence of cardiac damage attributable to electric stimulation.

*Case 11.* M. W. (B.C.H. No. 1458085), an 83 year old woman with complete heart block and auricular fibrillation for over one year, was admitted to the Boston City Hospital because of congestive heart failure. Following a debilitating pneumonia, her idioventricular rhythm slowed to 15 beats per minute and she suffered repeated syncopal attacks due to ventricular standstill. These increased in frequency despite the administration of ephedrine and epinephrine in oil.

External electric stimulation during complete heart block was effective, but could not be continued, because it was too painful. Therefore, it was decided to apply the stimuli as a resuscitative measure at the onset of syncope. During a subsequent syncopal attack, external stimulation immediately produced synchronous pulse beats and consciousness returned at once. One hour later, however, the patient was found dead.

*Case 12.* B. B. (B.I.H. No. M42598), an 84 year old man, entered the Beth Israel Hospital because of repeated Stokes-Adams attacks. Electrocardiograms showed normal sinus rhythm with prolonged and variable P-R intervals, and atrioventricular nodal rhythm.

External electric stimuli were applied for several short periods and the threshold voltage for effective cardiac stimulation was determined. The stimuli were observed to be effective during both normal sinus rhythm and atrioventricular nodal rhythm: they replaced the spontaneous rhythms with externally-paced ventricular complexes and synchronous pulse beats.

The pacemaker was kept ready for use but syncope did not recur. The patient was discharged on the fourteenth hospital day without further stimulation. Major syncopal attacks have not recurred for seven months.

*Case 13.* J. K. (B.I.H. No M43138), a 73 year old man with complete heart block for one month, entered the Beth Israel Hospital because of repeated Stokes-Adams attacks over a four-day period.

External stimuli were applied only for a few minutes; effective cardiac stimulation was observed during complete heart block and the threshold voltage of the stimuli was determined. The electrodes were then left in place on the chest for several days with the pacemaker in readiness for use in case of recurrent syncope. However, the patient had no more attacks and was finally discharged on the thirty-first hospital day without further stimulation. Major syncopal attacks have not recurred for eight months.

*Case 14.* J. C. (Mt. A.H. No. 104138), a 65 year old man with complete heart block, entered the Mt. Auburn Hospital twice in one month because of repeated syncopal attacks. Each time, external electric stimulation was tested during idioventricular rhythm. Excessive disturbance from these stimuli prevented satisfactory pulse observations, and the electrocardiograph was unsuitable. Therefore, stimulation was not continued; whether it produced cardiac responses was not determined. The patient died of cerebral damage eight hours after a prolonged episode of circulatory arrest.

The clinical course of this patient was uninfluenced by the attempts at external stimulation of the heart. He represents the only failure in this series to demonstrate effective cardiac stimulation. In this patient, early in our experience, the excessive disturbance from the stimuli was not adequately controlled by sedation. Furthermore, the electrocardiograph had a condenser-coupled input circuit which was found subsequently to be the cause of the difficulty in recording.

## Discussion

All 14 of these patients with syncope had Stokes-Adams disease*: complete or partial

* We have followed the suggestion of Parkinson, Papp and Evans in calling this condition a disease rather than a syndrome.[2]

atrioventricular block was present in each case; syncopal attacks were due to ventricular standstill, very slow idioventricular beats, ventricular tachycardia, ventricular fibrillation or combinations of these mechanisms.

External electric stimulation was demonstrated electrocardiographically to be effective in 13 of these 14 patients; its efficacy in the fourteenth patient was not determined. Each effective stimulus produced a ventricular complex; variations in rate and short interruptions of stimulation, as well as stimulation at subthreshold voltages, demonstrated that this relationship was not coincidental. Effective stimulation was applied during normal sinus rhythm, atrioventricular nodal rhythm, partial heart block and complete heart block with idioventricular rhythm. The interruption of these rhythms by the externally-paced ventricular complexes was additional evidence of the effectiveness of external stimulation.

External electric stimulation was applied in all 13 patients with Stokes-Adams disease because they had suffered recent syncopal attacks. In every instance the threshold voltage of effective stimuli was determined. Then, continuation of stimulation and its duration depended upon several factors: the frequency and severity of syncope, the nature of the spontaneous ventricular activity, and the tolerance of stimulation by the patient. In two of these patients stimulation was not continued after the threshold was determined; the remaining 11 patients were treated with short or prolonged periods of further stimulation.

*Untreated Group.* In two patients (cases 12, 13) the syncopal attacks were relatively infrequent and mild; the ventricular rhythms were regular and persisted at adequate rates; and stimulation produced moderate discomfort. Accordingly, after the thresholds of effective stimulation were determined, it was decided to keep the cardiac pacemaker in readiness for immediate use in case of recurrent syncope. Treatment with the pacemaker was not necessary thereafter, since syncope did not recur.

*Short Treatment for Individual Stokes-Adams Attacks.* In five additional patients it was also decided to reserve the pacemaker for their resuscitation from syncopal attacks. The disturbance produced by stimulation (cases 2, 8, 10, 11) and our limited experience (case 4) led to this decision even though the syncopal attacks were frequent or severe and the ventricular rhythms unstable.

Syncope due to ventricular standstill or very slow idioventricular rate was terminated immediately by stimulation. This striking response was observed countless times over a three-day period in case 4.

Paroxysms of irregular ventricular tachycardia or ventricular fibrillation were not stopped by stimulation (fig. 2*e*, cases 2, 8, 10). Whenever the irregular tachycardia stopped spontaneously, however, stimulation was immediately effective and shortened the period of ventricular standstill which occasionally followed.

For two reasons, the decision to treat individual Stokes-Adams attacks with short periods of stimulation involves the risk of fatality. First, the state of unfailing readiness for emergency stimulation that is necessary to avoid fatal delay in case of persistent ventricular standstill is impractical at the present time even in a hospital. Second, an attack of irregular ventricular tachycardia which is unaffected by stimulation may persist and be fatal. In view of the changing mechanisms of syncope often seen in these patients, the risk of persistent tachycardia is present even when standstill has been the predominant cause of syncope.

*Prolonged Treatment.* Because of the risk of fatality inherent in the short treatment of individual Stokes-Adams attacks, it is preferable to continue treatment beyond the time of resuscitation when syncope is frequent or severe and the ventricular rhythms are unstable. Furthermore, after resuscitation, continued stimulation is mandatory if an adequate spontaneous ventricular rhythm fails to appear when stimulation is stopped. Prolonged stimulation was applied in nine patients for periods of 25 minutes to 108 hours; in five patients (cases 1, 3, 4, 5, 6) because of ventricular standstill or very slow idioventricular beats; in three (cases 7, 8, 9) because of irregular ventricular tachycardia; and in one

(case 2) because of combinations of these mechanisms.

During persistent ventricular standstill or very slow idioventricular beats, continued stimulation after resuscitation maintained an adequate circulation and consciousness. Although slight transient depression of ventricular pacemakers was frequently observed following brief stimulation during idioventricular rhythm (fig. 3*b*), prolonged stimulation during ventricular standstill did not prevent the reappearance of spontaneous sustained pacemakers. In all patients but one (case 5), adequate sustained beats finally reappeared and stimulation was then stopped. An improved myocardial status resulting from the more adequate externally-paced rate may favor this recovery. On the other hand, the conditions producing standstill may be reversible and, when the patient is kept alive by the external pacemaker, recovery may occur either spontaneously or as a result of drug therapy.

Drug therapy may be useful at times in arousing and maintaining spontaneous ventricular pacemakers at adequate rates. We have occasionally observed these effects following the administration of ephedrine intramuscularly, and epinephrine and norepinephrine intravenously. Multifocal ventricular activity was produced by the intravenous administration of both epinephrine and norepinephrine; they must therefore be used cautiously.

The ability to sustain life in patients with Stokes-Adams disease by means of the external cardiac pacemaker has provided a heretofore unavailable opportunity to study quantitatively the effects of drugs on the ventricular pacemakers and to clarify some of the mechanisms of the disorder.[3]

Although stimulation did not resuscitate patients from paroxysms of irregular ventricular tachycardia, its continued application maintained a regular, externally-paced rhythm for long periods without interruption by ectopic ventricular activity. In two patients, (cases 2, 7) ventricular irritability finally subsided and stimulation was then stopped. One of these patients (case 7) died from a subsequent Stokes-Adams attack. In the two other patients (cases 8, 9) control of the ventricular irritability was never complete and both died.

*Untoward Effects of Stimulation.* No untoward cardiac effects of external electric stimulation were observed in these 13 patients. *External* electric stimulation did not produce multiple ectopic ventricular beats or ventricular fibrillation, effects that are seen experimentally in *direct* electric stimulation of the heart.[4] Necropsies in five patients showed no evidence of damage from stimulation to the heart or to neighboring structures. In two of these patients (cases 5, 7) there was damage resulting from intracardiac punctures; in one (case 5) cardiac tamponade was the immediate cause of death. The only tissue damage from stimulation consisted of superficial ulcerations under the chest electrodes in patients treated for a day or more. This problem has been minimized by frequent small changes in the positions of the electrodes.

The main untoward effects were chest pain and muscular twitch. The intensity of the pain and of the muscular contraction varied in different patients; in some it was negligible, in others it made continued stimulation difficult. Meperidine hydrochloride or paraldehyde usually made the discomfort tolerable and permitted continued stimulation. The administration of a curare-like drug (case 3) and local infiltration with procaine hydrochloride under the electrodes were ineffective. With prolonged stimulation the severity of the pain usually diminished and less medication was required.

On one occasion (case 8) an unusual effect on respiration was observed. When both electrodes were placed lower than usual on the chest, on the seventh or eighth intercostal spaces in the anterior axillary lines, stimulation produced apnea. When the electrodes were moved higher, to the fourth or fifth intercostal spaces, this interference with respiration stopped.

*Resuscitation from Unexpected Circulatory Arrest.* Circulatory arrest may occur unexpectedly during anesthesia. Like Stokes-Adams attacks, these episodes also represent desperate emergencies for which present therapy is often dangerous and ineffective. The mechanisms of unexpected circulatory arrest are ventricular

standstill or fibrillation; standstill is the more frequent cause.[5, 6, 7]

The success of external electric stimulation in arousing the heart from ventricular standstill in patients with Stokes-Adams disease suggested its value in resuscitating patients from unexpected circulatory arrest. We have established the effectiveness of external cardiac stimulation during experimentally-produced ventricular standstill.[3] Marked cardiac slowing and hypotension were produced by vagal stimulation; during asystole lasting as long as 37 seconds, the external cardiac pacemaker evoked heart beats adequate to restore the blood pressure to normal.

Because of its efficacy, safety and ready applicability, external cardiac stimulation appears to be the method of choice for the immediate treatment of a patient with unexpected circulatory arrest. If the cardiac mechanism is ventricular standstill, as is usually the case, and if the myocardium is still responsive, resuscitation should be successful. If the cardiac pacemaker fails to resuscitate the patient, the chest must be opened at once, the heart massaged, and appropriate drugs administered. If ventricular fibrillation is present and persists, electrical defibrillation across the exposed heart should be attempted. On the occasions when ventricular standstill follows successful defibrillation, the external pacemaker may be used.

In addition to electric stimulation of the heart, electric defibrillation of the ventricles has been accomplished experimentally across the unopened chest.[3, 8, 9] At present, however, external defibrillation is not feasible clinically because of the size of the equipment and the large current required. Studies of this problem are in progress.

## Summary

External electric stimulation was applied in 14 patients with Stokes-Adams disease; it was effective in 13. It was used in the treatment of recurrent syncope in 11; in two patients syncope did not recur. Six of the 11 treated patients were resuscitated from one or more Stokes-Adams attacks; 9 were treated for prolonged periods. Five patients survived following treatment for intervals of 9 days, 9 days, 7 months, 10 months and 12 months, respectively. Such long survivals without recurrent syncope suggest that the periods of cardiac disturbance which cause syncope may subside if the patient is kept alive during the crucial period.

Ten of these 14 patients have now died. In eight, death was clearly due to a Stokes-Adams attack: external stimulation was not applied terminally in three; it was applied after irreversible cerebral damage had occurred in two; and it was ineffective in three, presumably because the attack was due to persistent irregular ventricular tachycardia.

External electric stimulation resuscitated patients from attacks due to ventricular standstill; it maintained an adequate circulation during persistent ventricular standstill; and it prevented the recurrence of irregular ventricular tachycardia.

## Acknowledgments

We are indebted to the following doctors for permission to report some of the cases presented: Dr. J. A. Goldman (case 1); Dr. M. I. Abrams (case 2); Dr. W. B. Castle (cases 3, 6, 9 and 11); Dr. G. W. Thorn (case 7); Dr. N. Sidel (case 8); Dr. H. A. Derow (case 13); and Dr. D. Hurwitz (case 14). We are grateful to the house officers and nurses of the Beth Israel, Boston City, Mt. Auburn and Peter Bent Brigham hospitals for their efforts in the care of these patients.

## Sumario Español

Estímulo eléctrico externo fué aplicado a 14 pacientes con la enfermedad de Stokes-Adams; fué efectivo en 13. Fué usado en el tratamiento del síncope recurrente en 11; en 2 pacientes el síncope no recurrió. Seis de los 11 pacientes tratados fueron resucitados de uno o más ataques Stokes-Adams; 9 fueron tratados por tiempo prolongado. Cinco pacientes sobrevivieron luego del tratamiento por intervalos de 9 días, 9 días, 7 meses, 10 meses y 12 meses respectivamente. Estas supervivencias prolongadas sin síncope recurrente sugieren que los períodos de disturbio cardíaco que causan el síncope pueden apaciguarse si el paciente se mantiene vivo durante el período crucial.

Diez de estos 14 pacientes han muerto. En 8, la muerte se debió claramente a un ataque Stokes-Adams: estimulación externa no se aplicó terminalmente en 3: se aplicó luego de daño irreversible cerebral haber ocurrido en 2: y fué efectivo en 3, posiblemente debido a que el ataque fué causado por una taquicardia irregular ventricular persistente.

Estímulo eléctrico externo resucitó pacientes de ataques debidos a pausas ventriculares: mantuvo una circulación adecuada durante la pausa ventricular persistente; y evitó la repetición de taquicardia irregular ventricular.

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# Treatment of Abdominal Aortic Aneurysm by Excision and Replacement by Homograft

*By* HENRY T. BAHNSON, M.D.

Fourteen patients with arteriosclerotic aneurysm of the abdominal aorta are described. Excision of the aneurysm and reconstruction by an aortic homograft have been used in all cases. One patient from whom a ruptured aneurysm was excised, died after operation of uremia. Two other patients died of coronary artery disease after leaving the hospital. The remaining patients are well. Early results with this form of treatment are significantly better than those obtained by less definitive methods used in the past.

RECENT experiences with the treatment of saccular aneurysms of the aorta have shown that excision of an aneurysm in any portion of the aorta, with aortic suture, is feasible and that operative risk is not great.[1] Aneurysms of the distal abdominal aorta are in a more favorable position for surgical attack; however, such lesions are almost always caused by arteriosclerosis. The generalized distribution of the causative disease, the age of most persons affected, and the variable prognosis of untreated patients all indicate a more cautious approach in the application of excision in the treatment of arteriosclerotic aneurysms of the abdominal aorta. Nevertheless, the early results with excision of the aneurysm and replacement by homograft are encouraging and seem to establish this as a method of choice when operative treatment is indicated. This paper is a review of the first 14 patients treated by this procedure.

The great majority of aortic aneurysms are caused by either syphilis or arteriosclerosis. Occasional aneurysms caused by trauma or bacterial infection resemble in most respects those caused by syphilis. Syphilitic aneurysms are found most commonly in the thoracic aorta and predominantly in the ascending arch; they occur in younger persons usually less than 55 years of age; they are largely saccular aneurysms resulting from a localized rupture. Arteriosclerotic aneurysms, on the other hand, almost invariably occur in the terminal aorta below the origin of the renal arteries. As with other manifestations of arteriosclerosis, the lesion is more common in males and occurs in the older age group, the average age being around 65 years. Most arteriosclerotic aneurysms are fusiform, eccentric dilatations with elongation and thinning of most of the circumference. They rarely produce erosion of the vertebral bodies. The reason for the characteristically different location of syphilitic and arteriosclerotic aneurysms is not clear; however, the almost invariable localization of arteriosclerotic aneurysms in that portion of the aorta distal to the renal arteries is a fortunate feature from the surgical point of view.

The relative incidence of syphilitic and arteriosclerotic aneurysms varies with the prevalence of syphilis in any community. Likewise it is to be expected that in the future the frequency of syphilitic aneurysms will diminish because of the better control of syphilis, whereas that of arteriosclerotic aneurysms will increase with the increased duration of human life. At Hahnemann Hospital in Philadelphia, Maniglia and Gregory have shown that the number of aortic aneurysms per thousand autopsies has remained relatively constant since 1906, but that the ratio of arteriosclerotic to syphilitic aneurysms has increased from 1 to 8 between 1906 and 1931 to 2½ to 1 between 1949 and 1951.[2]

## CLINICAL FEATURES

The clinical characteristics of this group of patients are presented in table 1. All of the 14 patients had been aware of abdominal throb-

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bing and a mass. Most of them had a sense of fullness in the abdomen. In no instance was throbbing or fullness a distressing complaint. One half of the patients had significant pain which was attributed to the aneurysm and which has been relieved by excision of the lesion; in six of the seven the pain was associated with loss of weight or necessitated the use of narcotics. The pain was usually described as a steady deep ache, sometimes throbbing; it was not related to bending or straining, although frequently worsened or relieved by varying positions. The pain was usually referred to the midabdomen, although in some it has been entirely localized to the low back with radiation down the thighs. Pressure on the aneurysm has frequently elicited similar pain. The two patients observed after rupture of an aneurysm complained of severe pain; only one had pain before rupture. Seven patients had no pain at the time of hospitalization, although in five of these pain had previously been a significant complaint. Two patients (J. R. and M. A.) experienced an initial sudden pain in the abdomen at a time when the aneurysm probably first appeared. Patient J. R., a carpenter, was struck in the abdomen by a brace as the bit broke through a plank. An abdominal mass appeared which had not been noted during an examination for insurance two weeks before. The mass was tender and associated with moderate gastrointestinal hemorrhage. At operation the aneurysm was sharply delimited and there was only moderate arteriosclerosis in the adjacent vessel. This is the only patient in this group who had a definite history of causative trauma. In nine patients the asymptomatic aneurysm was discovered during examination for other reasons; in six of these nine patients symptoms appeared later.

## Diagnosis

Although aneurysms have been confused with almost every intra-abdominal and retroperitoneal lesion, the diagnosis is usually not difficult. On the other hand, the mere presence of a pulsating hard abdominal mass is not diagnostic, and other possible diagnoses must be eliminated. The expansile nature of the pulsation has been given as an important diagnostic feature; some authors have suggested attaching semaphores to the abdominal wall to observe separation of the tips with expansion. One only need see aortograms of these patients to realize the fallacy of this point, for most of the aneurysmal enlargement is filled with inelastic clot and the lumen is nearly normal.

Of much more value in diagnosis is the presence of a rim of calcium in the wall of the aneurysm, often well seen in the lateral or supine roentgenogram. In no instance in this series of arteriosclerotic aneurysms have vertebrae been found to be eroded. In doubtful cases aortography is useful for diagnosis as well as for evaluation. In one patient, F. S., the diagnosis could not have been made preoperatively without the aid of aortography. This patient had been extensively studied because of abdominal pain. Upon abdominal exploration elsewhere,* with a tentative diagnosis of pancreatic carcinoma, an aneurysm was found and an aortogram made. He was later referred to the author for definitive therapy. Even when the diagnosis was known the mass could not be felt in the unanesthetized patient.

The author has found aortography to be helpful although not essential. The information thus gained concerning the level and the extent of the aneurysm, the presence or absence of clot, and the size of the aortic and iliac arterial lumina are of importance in evaluating the indications for operation and in predicting the extent of excision required. General anesthesia with Pentothal and sometimes nitrous oxide has been used for this diagnostic procedure; the contrast medium employed was either Urokon or Diodrast injected through a long needle into the aorta. No significant difficulties were experienced with this procedure in this small group of patients.

## Prognosis

The prognosis for patients with untreated arteriosclerotic aneurysm is poor. The best study of this aspect is that of Estes.[3] He reported 102 patients with an abdominal aneu-

* By Dr. Stanley Hoerr, Cleveland Clinic.

rysm, 97 of which were attributed to arteriosclerosis, and three additional ones were caused by arteriosclerosis associated with syphilis. Survival in this group was compared with life expectancy of the normal population of the same mean age. Whereas 35 per cent of that portion of the normal population which is 65 years of age will die within eight years, 33 per cent of Estes' patients with abdominal aneurysm died within one year and 90 per cent within eight years. None of the eight patients who could be followed lived for 10 years. Of the 49 patients in whom the cause of death could be determined, 63 per cent died from rupture of the aneurysm. Applying this percentage to those with aneurysm who died, one can estimate that 2 of 10 patients with abdominal aneurysm will die from rupture of the aneurysm

TABLE 1.—*Clinical Findings and Surgical Procedures in 14 Patients with Abdominal Aortic Aneurysm*

| | Age Sex | Known Duration | History | Complications | Preoperative lumen and sac. | Operation and Date | Period of Occlusion, Minutes | Remarks and Follow Up Oct. '53 |
|---|---|---|---|---|---|---|---|---|
| 1. S.S. | 69 M | 18 mo., mass. | Asymptomatic. Mass noted at time of coronary infarction; recently enlarged. | Old coronary infarction. |  |  2-14-53 | 110 | Postoperative oliguria for 3 days. Now well. |
| 2. E.L.P. | 59 M | 3 yrs., mass. | Epigastric fullness, constipation and "gas" for 10 yrs. Attacks of paroxysmal tachycardia. | Possible coronary infarction 10 yrs. prior. |  |  3-9-53 | 80 | Postoperative oliguria. NPN rose to 218 mgm%. Now fully recovered. Non-specific symptoms improved. |
| 3. I.J. | 61 M | 8 mo., mass. | Asymptomatic till 4 days before admission; then severe pain in abdomen and back. | Hypertension 220/110 |  |  3-13-53 | 125 | Had been studied in 1952. Returned with early rupture. Now well except for hypertension. |
| 4. G.B.* | 74 M | 3 yrs., mass and pain | Continuous pain in abdomen and back for 1 yr. with 15 lb. weight loss. Asymptomatic for last 4 mo. | Amputation 1936 for Buerger's disease; claudication in remaining leg. 2 prior coronary infarcts. |  |  3-20-53 | 115 | Postoperatively distal pulses weak, calf tenderness. Amputation done 6 mo. later for ulcer and atrophy. Otherwise well. |
| 5. J.R. | 66 M | 6 mo., pain, bleeding, laparotomy | Sudden onset after trauma; g.i. hemorrhage required laparotomy. Subsequently quiescent. | Good general health. |  |  4-13-53 | 70 | Uncomplicated course. Excellent health now. |
| 6. J.K. | 70 M | 3 mo., pain and mass. | Increasing pain in abdomen, low back and right hip. | Hypertensive. Treated cardiac decompensation. |  |  4-16-53 | 60 | Ureter divided inadvertently and repaired. Loose clot in aneurysm probably dislodged. Bilateral amputations. Fatal acute myocardial infarction 6 mo. later |
| 7. T.F. | 77 M | 9 mo., mass. | Fullness, throbbing, increasing size. | Treated peptic ulcer. Good health. |  |  4-24-53 | 70 | Rapid recovery. Excellent health now. |

*Negro

TABLE 1.—*Continued*

| | Age Sex | Known Duration | History | Complications | Preoperative lumen and sac. | Operation and Date | Period of Occlusion, Minutes | Remarks and Follow Up Oct. '53 |
|---|---|---|---|---|---|---|---|---|
| 8. M.A. | 59 F | 3 mo., pain | Initial pain and mass. Asymptomatic since then. | Hypertensive, over 200 mm. Hg for 20 yrs. |  |  5-1-53 | 50 | Postoperative re-exploration for intestinal obstruction. Coronary infarction in hospital. Now well though slow to regain strength. |
| 9. I.M. | 55 M | 6 wks., pain and mass. | Increasing abdominal and back pain. Recent weight loss. | None. |  |  5-25-53 | 110 | Postoperative pain in leg for several months; good pulses and circulation. Now well. |
| 10. J.T. | 63 M | 1 yr., mass. | Low back pain 6 mo., much worse 6 wks. radiating to thighs. Wt. loss. Aneurysm tender; pressure caused pain in back and thigh. | Intermittent claudication. |  |  5-25-53 | 110 | Postoperatively no left femoral pulse. Later amputation. Died 4 mo. later of progressive myocardial failure from coronary artery disease. |
| 11. J.M. | 70 M | 2 yrs., mass. | Pain in low back 4 mo. requiring narcotics. 7 lb. weight loss. | None. |  |  8-3-53 | 105 | Pain relieved. Convalescing satisfactorily. |
| 12. F.S. | 48 M | 8 mo., pain | Pain in back and right lower quadrant. Aneurysm found at exploratory laparotomy elsewhere. | Treated gastric ulcer. |  |  8-4-53 | 70 | Smooth course. Now in good health. |
| 13. W.K.* | 46 M | 1 yr., pain | Intermittent abdominal pain 1 yr.; worse for 6 mo. Sent home to await graft. Returned with rupture of aneurysm. | Old uveitis. |  |  8-9-53 | 150 | Emergency operation with patient in shock. Renal arteries occluded 110 min. Postoperative oliguria. Died with uremic convulsions 86 hrs. after operation just after beginning diuresis. |
| 14. M.E. | 56 F | 3 yrs., mass. | Nausea, like "morning sickness." No pain. | Intermittent claudication 2 yrs. No pulses below femoral. |  |  9-18-53 | 110 | Nausea relieved. Convalescing satisfactorily. |

*Negro

in the first year after being seen, and half will die within eight years (fig. 1). If this cause of death can be excluded, the death rate from other causes is only slightly higher than that of the normal population.

The prognosis for an individual patient cannot be accurately predicted on the basis of any known sign or symptom. Pain is not reliable, as an aneurysm may be painless prior to rupture, and some painful aneurysms may exist for several years without change. In some instances severe pain has ceased without treatment or apparent change in the aneurysm.

## METHODS OF TREATMENT

Numerous methods have been used in treatment of aortic aneurysm. Those of more than passing interest may be grouped under the following headings: use of fibrogenic or reinforcing materials about the aneurysm, intro-

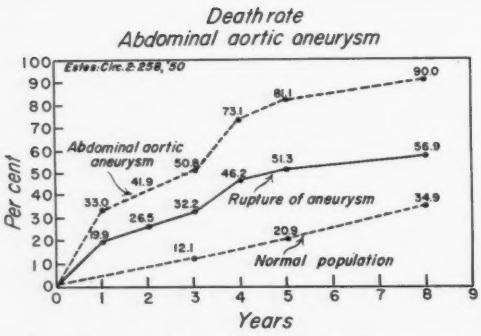


FIG. 1. Data obtained from Estes.[3] Upper curve and figures are from follow-up of 102 patients with abdominal aneurysms. Lower curve is estimated from life insurance data. Middle curve computed from top curve and Estes observation that of 49 patients in whom the cause of death was determined, 63.3 per cent died of rupture of aneurysm. Middle curve is important one for estimation of prognosis of aneurysm itself.

duction of wire into the aneurysm, ligation, endoaneurysmorraphy, and resection.

1. *Fibrogenic* and *reinforcing* materials have been used widely in recent years, based upon Page's original use of cellophane about the kidney to produce hypertension.[4] The active fibrogenic ingredient of this material has been shown by Yeager and Cowley[5] to be dicetylphosphate. Methods have been described for obtaining a high concentration of this agent about the aneurysm.[6] From experimental and clinical work performed here it seems probable that fibrogenic material placed about an aneurysm does not actually cause constriction with contraction but rather simply reinforces the wall with scar tissue. Assuming this to be true, the use of a porous material through which capillaries can grow offers advantages. Kirklin and associates reported 18 patients in whom the aneurysm was completely mobilized and the wall reinforced by a nonreacting polyvinyl sponge. Complete mobilization was often difficult, and survival with this treatment was no better than that of patients without operative treatment.[7] There have been numerous single case reports of the successful treatment of aortic aneurysm by wrapping, but in larger series results are not encouraging when the variable prognosis without treatment is recalled.

2. *Wiring* as a method of treatment of aortic aneurysm has undergone many modifications since Moore first introduced it in 1864.[8] One modern refinement of this method has been described by Blakemore and King[9]; they used fine, insulated, coin-silver wire which could be heated after introduction into the aneurysm. Such wire attains a temperature which induces clotting only in those areas of the vascular channel where flow is not so rapid, thus producing a selective concentric clotting and reinforcing the peripheral or saccular components of the aneurysm.

3. *Ligation* would seem to be applicable only to those aneurysms which occur in the terminal aorta. The danger to the patient and to his extremities from abrupt ligation of the aorta is considerable. The need for gradual occlusion of the aorta has been recognized for many years, and numerous methods to bring this about have been developed, including Halsted's aluminum bands, elastic ligatures, repeated operations with progressively tighter constriction, and the use of fibrogenic material. Forty-five attempts to occlude the aorta by ligation were recorded prior to 1951.[10] In none of the 21 instances recorded before 1918 did the patient survive. Since that time half of the patients so treated survived for six months and several for over a year. Blakemore devised a method for constriction of the aorta above the aneurysm, using an elastic band which he placed over fibrogenic polyethylene; he inserted wire into the aneurysm itself to induce clotting. This method of ligation was used in 33 instances. Those four patients in whom the aorta was completely obstructed obtained relief of pain and had no further progression of the aneurysm. When such a degree of constriction was not obtained the aneurysm remained a threat to the patient. Some patients with complete occlusion of the aorta, however, showed evidence of inadequate circulation to the lower extremities.[11] Hence ligation, while feasible in many instances, is associated with considerable risk and aims at an end result which is not entirely desirable.

4. *Endoaneurysmorraphy*, as described by Matas,[12] is an established procedure for treatment of aneurysm of peripheral arteries. Early

experiences with this method applied to the aorta were not successful, but recently Wiley,[13] and Kirklin[7] and their associates have combined this procedure with endarteriectomy and removal of clot and diseased intima. Of four patients operated upon by Kirklin only two were alive 8 and 14 months, respectively, after operation. The additional step, as described by Kirklin, of reinforcing such a reconstructed vessel by fascia or polyvinyl sponge has not improved the poor results.

5. For patients with aortic aneurysm in whom surgical therapy is indicated, the author believes *excision* of the aneurysm to be the procedure of choice. The sharp localization of arteriosclerotic aneurysms to the distal aorta makes this lesion particularly accessible to excision and replacement by homograft. Arterial homografts have been used for numerous conditions, based upon their original use by Gross, Bill and Peirce[14] in patients with congenital heart disease. Oudot described resection of the aortic bifurcation for thrombotic occlusion and replacement by homograft.[15] Dubost first used a graft for reconstruction after excision of an abdominal aortic aneurysm.[16] Numerous workers have since reported similar procedures.[17] There is evidence, from both animal experiments and clinical use, that such homografts will continue functionally adequate considerably longer than the five-year period of follow-up now obtainable on Gross's first patient.[18]

## Excision and Replacement by Homograft

### *Operative Technic*

General anesthesia has been used. Either a midline or a left paramedian incision extending from xiphoid to midway between umbilicus and pubis is satisfactory. The small intestines are displaced to the right and the posterior peritoneum incised over the aneurysm to the left of the base of the mesentery (fig. 2). The peritoneum usually can be readily dissected free. Before attempting mobilization of the aneurysm, tapes must be placed beneath the aorta and the iliac arteries so that bleeding may be controlled if necessary. During the dissection around the proximal aorta, care must be exercised that the renal arteries and left renal vein are not damaged. Similarly the iliac and hypogastric veins must be avoided when isolating the adjacent arteries. The ureters should be visualized and avoided. The inferior mesenteric artery is frequently found occluded, but one need have little fear of ligating it if it is patent.

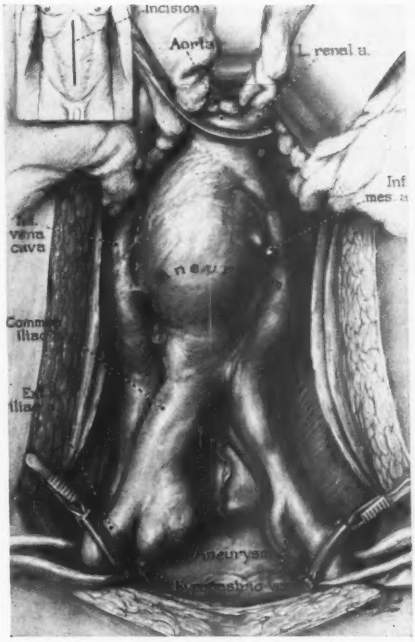


Fig. 2. Operative exposure of arteriosclerotic aneurysm through midline incision. Intestines and mesentery are displaced to the right. (Reproduced by permission of *Annals of Surgery*.[21])

As soon as the extent of the aneurysm and the condition of the iliac arteries distally can be determined, a homograft is selected and preparation of it begun. The graft used in case 1 was preserved at 4 C. in fluid as described by Gross, Bill and Peirce.[14] All others were frozen and dried. The latter method is advantageous in that such grafts may be kept indefinitely and seem to be associated with less danger of thrombosis.[19] Preparation of a frozen-dried graft usually requires 40 to 50 minutes, during which time further mobilization of the aneurysm from the vena cava and posteriorly can be done. This mobilization can best be performed after the aorta is divided and the aneurysm drawn forward (fig. 3). When excision is begun the aorta can be occluded with a curved Potts coarctation clamp, and the iliac arteries with rubbershod bulldog clamps or Potts ductus clamps. Despite care in dissecting the aneurysm from adjacent vena cava and iliac veins, these vessels have often been torn; the defects have been sutured with 5-0 arterial silk. It may be wiser to leave the wall of the aneurysm where it is intimately adherent. In this group of patients, however, a vigorous effort was made to remove the sac if possible because of

previous difficulties with infection in saccular aneurysms which were incompletely excised.[1] A small portion of the aneurysm was left in only one patient.

An extremely important step is the instillation of approximately 10 mg. of heparin into each distal iliac artery as soon as it is occluded. This can be done by needle injection of concentrated solution or through a catheter inserted into the artery and withdrawn as soon as the instillation of a diluted solution is made. In several instances when this step was delayed, it was necessary to express thrombi from the distal segment. Thrombosis may occur down to the entrance of the first collateral artery if heparin is not used, and this thrombus might be flushed distally when the graft is opened. Such has apparently happened in three patients in this series.

The graft was sutured with 4-0 arterial silk to the aorta and 5-0 silk to the iliac arteries. Because of the short cuff of aorta proximally, the anastomosis was made as described by Blalock, by placing a posterior row of continuous everting sutures which is pulled up when completed. The anterior portion and iliac anastomoses distally have been made with an over-and-over stitch through all layers (fig. 4). Competence of the proximal anastomosis can be tested by injection of saline into the graft through


FIG. 4. Reconstruction of aorta by homograft between aorta and common iliac arteries distally. (Reproduced by permission of *Annals of Surgery*.[21])

one iliac and additional sutures placed if required. In many instances the posterior row has been reinforced by a continuous over and over suture. When occlusion of the aorta is unduly prolonged one completed limb of a bifurcation graft may be opened, provided the remaining iliac is occluded at its origin to prevent thrombus formation in a short blind segment.

FIG. 3. Aorta has been occluded with curved Potts coarctation clamp, divided, and the aneurysm drawn forward. Mobilization and dissection behind the aneurysm are much easier at this time than before division of the aorta. (Reproduced by permission of *Annals of Surgery*.[21])

In all these patients the aorta was arteriosclerotic. This made anastomosis more difficult than in normal patients but not impossible. Frequently plaques were removed from the site of anastomosis before suturing was begun.

In elderly patients such as these one must follow fluid and electrolyte balance carefully in the postoperative period. Antibiotics were used to prevent infection. Gastric suction was employed to avoid the otherwise almost inevitable abdominal distention. No other precautions were taken in postoperative care. Early ambulation was urged and begun 24 to 48 hours after operation or as soon as the patient was willing.

*Results*

An aneurysm of the terminal aorta has been excised and replaced by a homograft in 14 patients. The procedure was completed in each instance.

There have been three deaths thus far in the group of patients: one at four days, and one each at four and five months after operation. The first of these, W. K., was known to have an aneurysm which extended above the level of the renal arteries. He had been sent home awaiting procurement of a long bifurcation graft but returned in profound shock because of rupture of the aneurysm. Massive transfusion therapy was given and operation begun. By rapid and blunt dissection in the large hematoma the superior mesenteric artery and aorta proximal to the renal arteries were isolated and occluded with a single clamp. The aorta was divided just below the renal arteries and a graft was sutured in place; the suture line partly involved the mouths of the renal arteries. The graft was occluded and blood was allowed to perfuse the kidney after completion of this anastomosis while the two iliac anastomoses were completed; renal flow was shut off for 110 minutes. He was beginning to diurese on the fourth postoperative day when death occurred following uremic convulsions. Autopsy showed advanced nephrosclerosis. The right kidney was considerably hydronephrotic with obstruction of the upper ureter from an old hematoma caused by a previous small leak. Renal ischemia from preoperative shock and hurried occlusion of the leaking aorta undoubtedly caused severe damage to the diseased kidneys. This is the only instance in this group of patients in which the aneurysms extended above the renal arteries, and in this case the aneurysm was believed to be due to syphilis as judged by histologic examination.

The second death (patient J. T.) occurred four months after operation; it was due to progressive myocardial failure due to coronary artery disease. Gangrene of the left foot occurred in the early postoperative period and supracondylar amputation had been necessary.

The third death (patient J. K.) resulted from acute myocardial infarction six months after operation. Bilateral amputation had been performed because of ischemic necrosis shortly after the initial operation.

A distressing complication has been diminution of the circulation to the legs which occurred to a significant degree in three patients. One required bilateral and a second unilateral amputation during the immediate postoperative period as mentioned above. The third (G. B.) recently returned because of atrophy of the calf and ulceration on the foot; amputation was performed. It is believed that the cause of ischemic necrosis in all three patients was dislodgment of a thrombus which formed in the distal iliac artery during occlusion and insertion of the graft. In these patients heparin was not administered as described above. It is now believed that the use of heparin is essential. The aorta was occluded for the longest period in the last two patients in the group. No permanent impairment of peripheral circulation occurred, although one patient had had prior intermittent claudication and occlusion of both superficial femoral arteries. Lumbar sympathectomy has been done in several instances but but there is no evidence that it is of definite value.

*Selection of Patients*

During the period that this procedure has been employed, only two patients seen have been refused operation. One was in her late eighties and in shock from rupture of the aneurysm; she subsequently died. The second was 74 years old and free of symptoms; the aneurysm extended above the renal arteries as determined by aortography. A 70 year old man would not permit operative treatment. On the basis of experience with these patients and the expected survival as discussed earlier, the following criteria serve as guides in the selection of patients for operation.

Chronologic age is of much less importance than physiologic age, but a young person with an aneurysm has a greater likelihood of dying because of the aneurysm than an older one. Patients 70 years of age or over without symptoms should certainly not be urged into operation. Cardiac compensation, renal function and the presence of coronary artery disease must be more carefully evaluated in elderly patients.

Pain and abdominal discomfort are the prime indications for operation. At any age operation is probably justified if discomfort cannot be controlled without the use of narcotics. Under such circumstances relief of pain furnished by excision of the aneurysm justifies the risk to life and limb. Two patients, J. T. and G. B., in whom ischemic necrosis developed and who required amputation were nonetheless grateful because of relief from pain.

Rupture of the aneurysm is an indication for emergency operation. Frequently there is a period after initial leakage when the patient recovers temporarily before the retroperitoneal hematoma extends or secondarily ruptures. One patient (I. J.) survived operation for an early rupture. The single patient who died following excision of a ruptured aneurysm would undoubtedly have died without operation.

Finally, the author has relied to a small extent upon the aortographic examination, believing that there is more danger of rupture from an aneurysm with a large lumen and a thin wall than from an aneurysm in which a thick, laminated clot reduces the lumen to nearly normal. In addition, irregularities of the lumen may indicate areas of potential weakness. Aortography will demonstrate the rare aneurysm which extends above the renal arteries. Such an aneurysm can be largely excised and aortic anastomosis can be done at the level of the renal arteries, but this is associated with an increased risk.

## Summary

Fourteen patients with an abdominal aortic aneurysm have been treated by excision of the terminal aorta and replacement by homograft. One patient, in whom the renal bloodflow had been occluded for 110 minutes, died of uremic convulsions four days after excision of a ruptured aneurysm. One patient died four months after operation of progressive myocardial failure due to coronary artery disease, and one died of coronary occlusion six months after operation. These last two and one additional patient required amputation because of ischemic necrosis. This was probably caused by dislodgment of a thrombus which formed in the distal iliac artery during occlusion of the homograft. Proper use of heparin during operation appears to prevent this complication.

The 11 surviving patients have remained in good health during the short periods of observation, which range from two to eight months.

Excision and replacement by homograft appears to be the procedure of choice for abdominal aortic aneurysm when surgical therapy is indicated.

## Acknowledgments

Patient I. J. was treated at The Marine Hospital, U. S. Public Health Service, Baltimore, with Dr. E. Converse Peirce, II. One of the frozen-dried grafts was obtained from the Tissue Bank, U. S. Naval Medical Center, Bethesda, Md.

## Sumario Español

Catorce pacientes con aneurisma de la aorta abdominal han sido tratados por excisión de la aorta terminal y reemplazo con homoinjerto. Un paciente en el cual la circulación renal fue ocluída por 110 minutos, murió con convulsiones urémicas cuatro días después de la excisión de un aneurisma rupturado. Un paciente murió cuatro meses después de la operación de desfallecimiento progresivo del miocardio debido a enfermedad coronario y uno murió de oclusión coronaria seis meses después de la operación. Estos últimos dos y un paciente adicional necesitaron amputación debido a necrosis isquémica. Esto se debió probablemente a desalojo de un trombo con origen en la arteria ilíaca distal durante la oclusión del homoinjerto. Uso apropiado de heparina durante la operación aparenta evitar esta complicación. Los once pacientes sobrevivientes han permanecido en buena salud durante el corto período de observación, que data de dos a ocho meses. Excisión con reemplazamiento con homoinjerto aparece ser el procedimiento más indicado para aneurisma aórtico abdominal cuando el tratamiento quirúrgico es necesario.

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# Further Observations on the Closure of Atrial Septal Defects

*By* Harris B. Shumacker, Jr., M.D., Harold King, M.D., and Paul R. Lurie, M.D.

Though patients with small atrial septal defects may do well, in certain individuals with large defects operative closure is highly desirable because of the resultant cardiac dysfunction and the poor prognosis without treatment. Extensive efforts in the experimental laboratory have led to the development of a number of methods for the surgical closure of these defects, a number of which have had clinical trial. An earlier method, in which a pericardial pocket was affixed to an incision in the atrial wall and invaginated into the atrial cavity so that its posterior wall could be sutured to the rim of the defect, proved safe and reliable in experimental animals. One case demonstrated, however, that in large human defects the pericardium may not become sufficiently rapidly vascularized to permit its survival. The present experiments have shown that the same technic modified by substitution of a plastic nylon pocket appears entirely satisfactory. In one clinical case it was applied with success. It is suggested that when simpler methods are not applicable this procedure may prove safer and more reliable than certain other methods which have been used.

EXPERIMENTAL efforts to close defects of the atrial septum surgically have previously been reported.[1] One method studied proved entirely reliable and appeared altogether suitable for use in human subjects. It involved fixing to an incision in the atrial wall a half-moon shaped pocket made of autogenous pericardium (fig. 1). This could be invaginated into the atrial cavity and through it one could palpate without difficulty the rim of the septal defect. The defect could then be snugly closed by suturing the posterior wall of the pocket to its margins. The procedure could be applied regularly in dogs with artificially created large atrial septal defects without mortality, without interference with cardiac function, without blood loss, and without danger of air embolism or intracardiac thrombosis. The autogenous grafts all survived and became firmly united with the margins of the septum. Closure was complete in all except a few animals, and in the exceptional cases the residual defect was inconsequential, being only approximately 1 mm. in diameter.

This method as finally developed was utilized in two human cases.[2] In both the operation was tolerated well. One showed marked clinical improvement, though postoperative catheterization studies revealed a persistent left-to-right atrial shunt. The other died suddenly five months after operation and postmortem examination demonstrated complete disappearance of the pericardial graft except for the area fused to the portion of septum anterior to the defect. This disappointing occurrence seemed explainable on the basis that the human pericardium, being considerably thicker than that of the dog, offers greater obstacles to revascularization, and that, furthermore, human atrial septal defects may be considerably larger than those created and treated in experimental animals, as was the case in this patient. An alternative explanation may be postulated on the basis of difference in ease and rapidity of healing of the graft to a fresh surgically produced canine defect and its vascularization as contrasted with the case of a congenital human defect. It was obvious, therefore, that the method required modification, and it was suggested that the use of pockets of inert plastic material instead of autogenous pericardium might render the procedure entirely satisfactory.

It is our purpose to describe the utilization of this modified procedure in experimental animals and in one human case.

The experimental observations were made on healthy mongrel dogs. Large atrial septal

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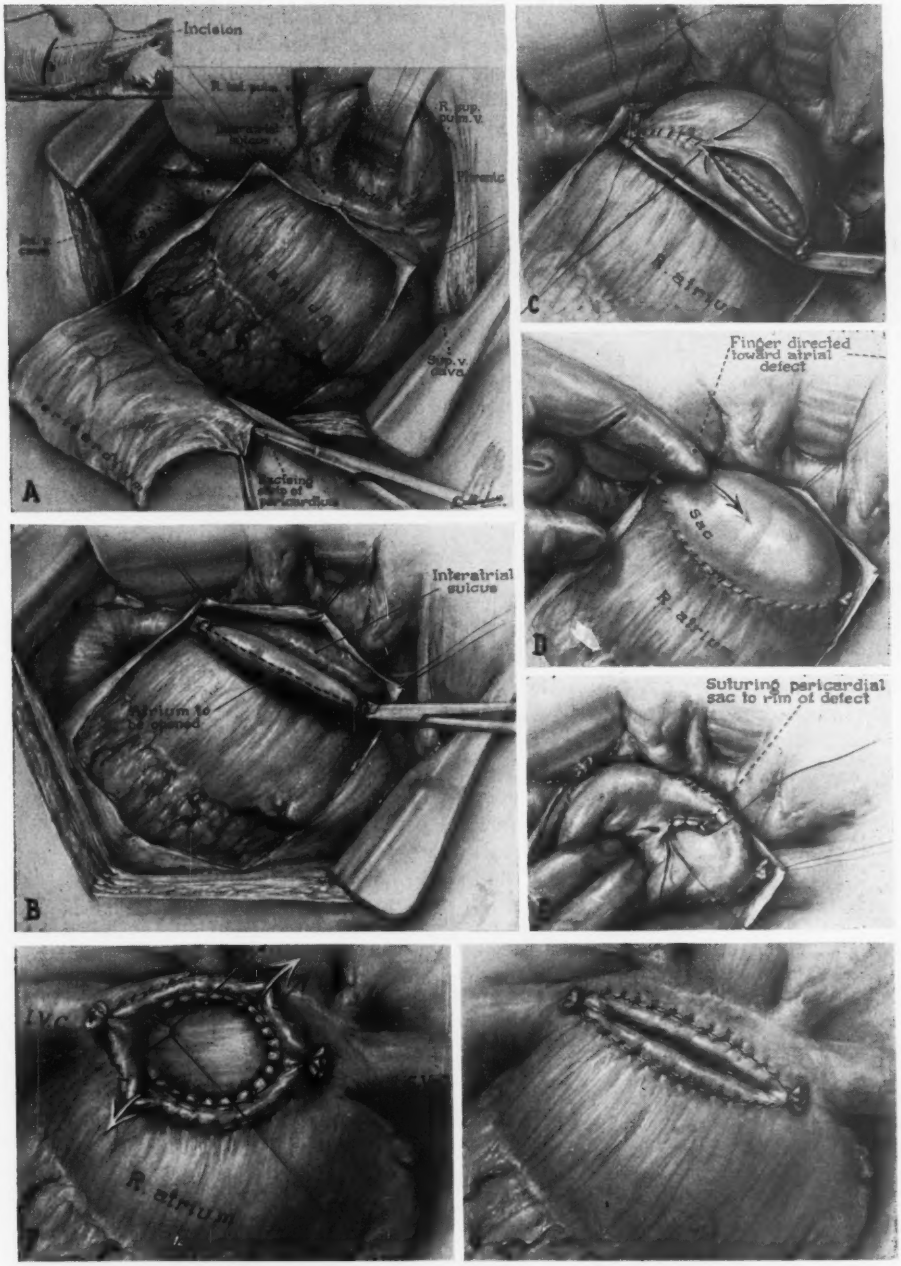


FIG. 1. Drawings illustrating the technic of repair of atrial septal defects, as applied to patients. (*A*) Operative exposure. The pericardium is being excised. (*B*) A clamp is placed on the atrial wall preparatory to its incision. (*C*) The pericardial pocket is sutured to the incision in the atrial wall. (*D*) On release of the clamp the pocket fills with blood. (*E* and *F*) Sketches from two cases showing the manner in which the pocket is invaginated into the atrial cavity and its posterior wall pushed back against the septum so it can be sutured to the margins of the defect. (*G*) The completed procedure. Drawings by Leon Schlossberg.

defects were surgically created by a previously described method[3] which results in near total defects that tend to remain widely patent during long periods of observation. At the same operation they were repaired by the invaginated pocket technic, differing from that originally presented only in the use of thin, finely woven nylon material instead of autogenous pericardium. These pockets were similar in size and shape to those which had formerly been made of pericardium. They were half-moon in shape and the open end was approximately 5.5 cm. in length. The nylon was soaked in sterile mineral oil immediately prior to its use. The edges of the nylon pocket could be sutured easily to the margins of the incision in the atrial wall. Upon release of the clamp from the atrial wall, blood filled the pocket and ballooned it out. Ordinarily there occurred for a moment some slight loss of blood through the thin nylon, but bleeding always ceased promptly and no significant loss occurred. The pocket was then invaginated into the atrial cavity. The margins of the defect could be clearly palpated so that the posterior wall could be firmly fixed to the rim of the defect with a continuous locking suture of 4-0 silk swedged onto a small round needle. When no clear septal rim remained, as was generally the case near the caudal posterior aspect of the septum, closure was supplemented by the use of several interrupted sutures passed from within the pocket out through the junction of the vena cava and left atrial wall and back through again into the interior of the pocket.

In all animals the septal defect was palpably closed. Thirteen dogs were treated in this manner. All tolerated the procedure and survived indefinitely. Ten have been sacrificed to date and their hearts examined (table 1).* Closure was complete in all save one and in the exceptional case the residual defect was only approximately 1 mm. in diameter. The period elapsing between operative repair and sacrifice of the animal ranged from 11 to 100 days. Two specimens examined 11 and 19 days after repair revealed the plastic material to be covered by a thin sheet of gelatinous material (fig. 2). Two other specimens examined 17 and 18 days after repair appeared to have good endothelial covering of the graft and this was the case in all of the specimens of longer duration. In no case were gross thrombi visible on the graft or in the atrial cavities. In no case was there obstruction of the coronary sinus or the vena caval ostia. No gross distortion of either atrium was visible, the graft simply having resulted in a thick, firm buttressing of the septum. The appearance of the healed septum was remarkably like that previously observed in cases of closure with autogenous pericardium (fig. 3).

TABLE 1.—*Observations on Closure of Experimentally Created Atrial Septal Defects in Dogs*

| No. of Animal | Interval in Days between Repair and Postmortem Exam. | Completion of Defect | Covering of Graft |
|---|---|---|---|
| 1 | 11 | Complete | Thin gelatinous membrane |
| 2 | 17 | Complete | Endothelium |
| 3 | 18 | Complete | Endothelium |
| 4 | 19 | Complete | Thin gelatinous membrane |
| 5 | 24 | Tiny defect 1 mm. drain | Endothelium |
| 6 | 46 | Complete | Endothelium |
| 7 | 53 | Complete | Endothelium |
| 8 | 63 | Complete | Endothelium |
| 9 | 65 | Complete | Endothelium |
| 10 | 100 | Complete | Endothelium |

## CASE REPORT

The patient was a 11 year old white boy in whom a diagnosis of congenital heart disease had been made at the age of 3 months. Cardiac symptoms had apparently not been noted until the child started to school at the age of 6 years. It then was evident that he became easily fatigued and had shortness of breath and a sensation of pounding of the heart when he tried to play with his friends, walk rapidly, or climb a slight grade. Shortly thereafter digitalis therapy was begun. This was continued until his first admission to the hospital in January 1953. The dyspnea on exertion, easy fatigability, and pounding of his heart had continued. He slept on one pillow. The patient and his parents were unaware of the presence of any cyanosis. For three or more months he had complained of transient precordial pain.

* Since submission of the manuscript the three remaining dogs have been sacrificed 177, 182 and 189 days, respectively, after repair. Closure was complete in all instances.

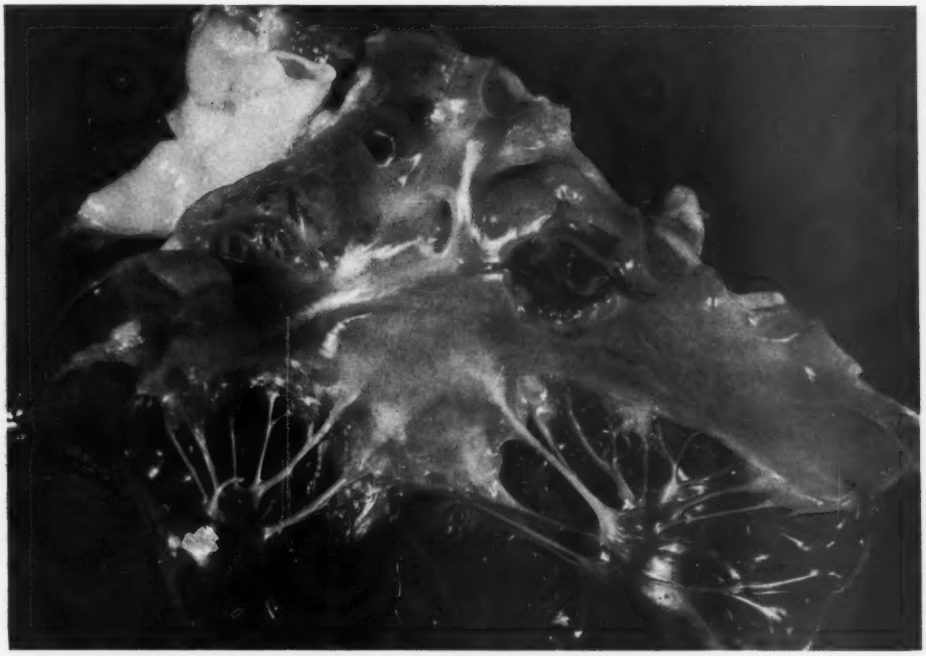

FIG. 2. Photograph of specimen 11 days after repair showing the closed septum from the left atrial cavity. The nylon graft is covered with a thin sheet of gelatinous material. In older specimens the area of repair is hardly distinguishable from the remainder of the septum.

He weighed 72 pounds and was 4 feet, 7 inches in height. There was a prominent precordial bulge. A strong systolic thrill was palpable most prominently over the pulmonic area. The pulmonic second sound was barely audible. A grade IV systolic murmur was heard over most of the precordium and throughout the chest. It was loudest in the pulmonic area. The liver was not palpably enlarged. Fluoroscopic and radiologic examinations of the heart revealed some increase in size with definite enlargement of the right ventricle. The main pulmonary trunk, the right and left pulmonary arteries and their smaller branches were all considerably enlarged. Electrocardiographic tracings demonstrated a normal sinus rhythm and evidence of right ventricular hypertrophy. Cardiac catheterization revealed evidence of mild pulmonary valvular stenosis with right ventricular hypertension and an atrial septal defect with large left-to-right and less pronounced right-to-left shunt.

He was returned to the hospital on May 18 for operative treatment. He weighed 71 pounds. Physical and laboratory studies were essentially the same. He was operated upon on May 21. Exploration was carried out through a right anterior fifth intercostal incision. The pericardium was opened parallel to the course of the phrenic nerve. The right atrium was markedly increased in size. The right pulmonary veins drained into the left

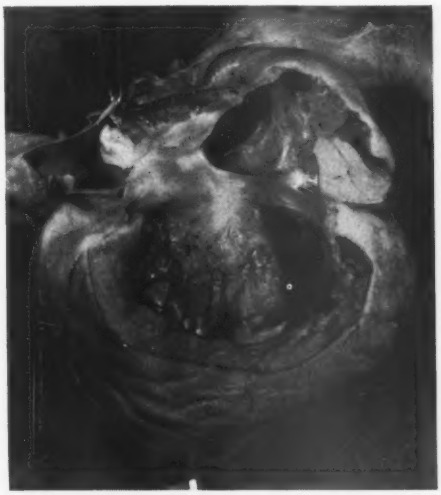

FIG. 3. Photograph of specimen 100 days after closure of atrial septal defect. A portion of the right atrial and ventricular walls has been removed. The widely open ostia of inferior and superior venae cavae and coronary sinus are seen. The graft is covered with glistening endothelium. Closure of the defect is complete.

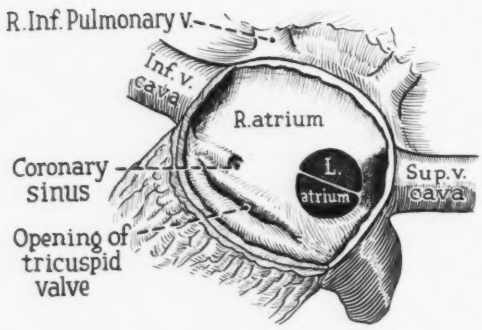


FIG. 4. Schematic drawing of the septal defect in patient treated by operative repair.

atrium. Those from the left were not seen. On palpating through the right atrial wall, one could feel a large atrial septal defect which easily admitted the index finger with room to spare. It was judged to be approximately 2 cm. in diameter. One narrow strand of tissue was felt to cross the midportion of the defect which was situated posteriorly adjacent to the posterior rim of the superior vena caval ostium. It was not found possible to invaginate the right atrial wall against the margins of the defect without at the same time producing obstruction of the superior vena cava.

A ridge of atrial wall adjacent to, and roughly parallel to, the interatrial groove was elevated with traction sutures and clamped with an angulated Glover clamp. An incision approximately 5.5 cm. in length was made and a half-moon shaped pocket made of thinly woven nylon was sutured to its edges. With release of the clamp there was only momentary trivial bleeding. The pocket was invaginated into the atrial cavity and the defect could be clearly felt. The posterior wall of the pocket was pushed against the defect and fixed to its rim with four equidistantly spaced interrupted sutures of 4-0 silk. Approximation of the nylon to the margin of the defect was completed with a continuous suture of the same material, interrupted in four places. There was a scant rim of septum cephalad, and practically no rim posteriorly at the base of the defect. It was felt that closure was complete, though there was some question about the completeness of closure at the posterior cephalad margin. The incision in the atrial wall was approximated with a continuous suture of 4-0 silk interrupted in one place. It was not felt necessary in this case to introduce a finger into the right atrial cavity through the appendage, a procedure which may be thought advisable in certain cases as an aid in suturing the pocket to the margins of the defect.

The patient withstood this procedure so well that it was felt safe to proceed with pulmonary valvulotomy. The incision was extended across the sternum and into the sixth intercostal space on the left. The left pleural cavity was not entered. The pericardial incision was enlarged so as to bring into view the large right ventricle and pulmonary trunk. After placing traction sutures in the right ventricular wall, a small incision was made through which Brock valvulotomes were passed. The stenosis was sufficiently great so that the smallest valvulotome was passed through the valve only with considerable force. The valve was further sectioned by passage of the larger instruments, following which it was thoroughly dilated by spreading the blades of a Kelly clamp. The pulmonary artery now pulsated well and the thrill was much coarser in quality. The pericardium was loosely approximated with interrupted silk sutures. The sternum was brought together with a few steel wire sutures. The ribs on the right side were approximated with two heavy catgut sutures and the remainder of the chest wall was closed in layers with interrupted silk sutures. The patient withstood the procedure well, the blood pressure and pulse remaining essentially stable throughout. Two hundred and fifty cubic centimeters of whole blood and 750 cc. of 5 per cent glucose were administered during the operation, which was completed in two hours. The endotracheal tube had been inserted under sodium pentothal and Anectine anesthesia, following which to-and-fro semiclosed ether anesthesia was used.

The patient had a relatively uneventful convalescence and was discharged from the hospital on June 5. Prior to discharge oximetry studies revealed the arterial oxygen saturation at rest to be 94 per cent. It rose to 98 per cent while the patient breathed pure oxygen.

He continued to do well and was readmitted on August 3. He and his parents stated that his appetite had been markedly improved since operation.

TABLE 2.—*Cardiac Catheterization Findings*

| | Before Operation | After Operation |
|---|---|---|
| Oxygen consumption, cc./min. | 237 | 191 |
| Systemic flow index, L./min. M.$^2$ | 5.1 | 3.8 |
| Pulmonary artery flow index L./min./M.$^2$ | 8.7 | 4.7 |
| Effective pulmonary flow index, L./min./M.$^2$ | 4.0 | 3.3 |
| Left-to-right shunt, L./min./M.$^2$ | 4.7 | 1.4 |
| Right-to-left shunt, L./min./M.$^2$ | 1.1 | .5 |
| Arterial oxygen saturation per cent | | |
| (a) breathing room air | 86.8 | 89.6 |
| (b) breathing pure oxygen (assuming 1.0 vol. % dissolved oxygen) | 92.6 | 94.5 |
| Pressure, mm. Hg | | |
| Right atrium | 7/3 | 7/3 |
| Main pulmonary artery | 22/5 | 40/8 |
| Right ventricle | 96/7 | 75/7 |

His height was now 4 feet, 9 inches, and he weighed 77 pounds. He had been entirely relieved of his exertional dyspnea, fatigability, pounding of the heart and precordial pain. He had been leading a normal active life and had taken no medication.

Electrocardiographic tracings showed evidence of right ventricular hypertrophy, but revealed a marked change as compared with the preoperative tracings. In contrast to the earlier records, there was less T-wave inversion in $V_1$ and $V_5$, and there were now normal ST-T segments in $V_2$, $V_3$, $V_4$ and $V_6$, and a normal left ventricular QRS complex in $V_5$ and $V_6$. Radiologic studies revealed no remarkable change.

Cardiac catheterization was repeated. Considerable improvement was noted. The data are shown in table 2. The pulmonary valvulotomy had been effective as shown by the fall in right ventricular pressure and the rise in pulmonary artery pressure. In spite of this there was marked reduction in left-to-right shunt. There was also reduction in right-to-left shunt.

When seen again on November 6, five and one half months after operation, he was free of symptoms. There was no visible cyanosis. The second pulmonic sound was distinct and clear.

Experience with this case suggests that the modified operation using a nylon pocket is well withstood since the patient tolerated the procedure so well that after its completion it was felt safe to extend the incision and perform pulmonary valvulotomy. During follow-up observations of five and one half months, the patient has been relieved of his cardiac symptoms, has an improved appetite, and is gaining in weight and stature. Postoperative catheterization studies suggest that a small residual shunt exists. At the time of operation it was felt that the closure was complete with the possible exception of the posterior cephalad margin of the defect where no true rim of tissue was present. In retrospect more secure closure in this position could undoubtedly have been obtained by passing one or more interrupted sutures from within the pocket out through the junction of the posterior wall of the vena cava and atrium and back again. Such maneuvers have been found in our experimental studies to add security to the closure wherever there is no true rim of the defect.

## Discussion

A modification of the original suggestion for repair of atrial septal defects by use of a pocket of thin, finely woven nylon instead of pericardium has been described. Experiences with this method in the surgical closure of experimentally created atrial septal defects in dogs and in one human patient are promising. It is felt that this method should prove safe and applicable to all types and sizes of atrial septal defects and in patients with small as well as those with large hearts.

As experience increases with the operative repair of defects of the atrial septum it is entirely likely that no single method will be found best for all cases and that, instead, a number of procedures will be utilized, selecting for each case that which can be most easily and safely carried out. Experiences suggest that many cases can be treated successfully by relatively simple measures which require no grafting, such as Murray's[4] original suggestion of approximating the anterior and posterior atrial walls by means of sutures passed through the septum, some modification of this principle like that proposed by Björk and Crafoord[5] or suture of the right atrial wall to the margins of the defect as practiced by Bailey and his associates.[6] Certainly for cases in which such methods do not seem applicable, the operative procedure described would appear to have advantages over others. In contrast to the atrial well method of Gross[7] it can be performed in a dry field. There is every reason to suppose it will prove much safer and simpler than methods of closure through the open right atrium during temporary occlusion of venous inflow under conditions of hypothermia[8, 9] or with use of an artificial pump-oxygenator apparatus.[10]

## Summary

1. An earlier procedure in which a pericardial pocket was sutured to an incision in the atrial wall and invaginated into the atrial cavity so that its posterior wall could be sutured to the margin of the defect proved safe and reliable in experimental animals, but in one patient the graft disintegrated presumably because of failure to undergo sufficiently rapid vascularization. This method has been modified by substitution of a pocket fashioned of inert plastic material: thin, finely woven nylon.

2. In experimental animals this procedure has been safe and effective. It was utilized in 13 dogs without mortality and with complete closure of the defect in all instances save one, the residual defect in the exceptional case being only 1 mm. in diameter.

3. The method has been used with satisfaction in the treatment of one patient with a large atrial septal defect and a pulmonic valvular stenosis.

4. It is suggested that this method may prove safer and more generally satisfactory than certain other methods in those clinical cases in which simpler methods are not applicable.

### Acknowledgment

The authors wish to express their appreciation to Mrs. M. Rice and Miss P. Brumbaugh for their invaluable assistance in the experimental operating rooms.

### Sumario Español

1. Un procedimiento anterior en el cual un bolsillo de pericardio se suturaba a una incisión en la pared atrial y se invaginaba en la cavidad atrial de manera que la pared posterior pudiera ser suturada al margen del defecto probó ser seguro y confiable en los animales experimentales, pero en un paciente el injerto se desintegró probablemente debido a falta de desarrollar vascularización lo suficientemente rápida. Este método se ha modificado por medio de substitución de un bolsillo diseñado de un material plástico inerte: nilón finamente tejido y delgado.

2. En animales experimentales este procedimiento ha sido seguro y efectivo. Se utilizó en 13 perros sin mortalidad y con cierre completo del defecto en todos los casos con excepción de uno, en el cual el defecto residual fué solamente de 1 mm. en diámetro.

3. El método ha sido usado con satisfacción en el tratamiento de un paciente con un defecto grande del septo atrial y una estenosis pulmonar.

4. Se sugiere que este método puede probar ser más seguro y generalmente mas satisfactorio que ciertos otros métodos en aquellos casos clínicos en que métodos más sencillos no son aplicables.

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# Circulatory Changes Produced by the Valsalva Maneuver in Normal Subjects, Patients with Mitral Stenosis, and Autonomic Nervous System Alterations

*By* H. D. McIntosh, M.D., J. F. Burnum, M.D., J. B. Hickam, M.D., and J. V. Warren, M.D.

The cardiac output has been measured during the immediate post-Valsalva maneuver recovery period in normal subjects, patients with clinically significant mitral stenosis, and patients with alterations of the autonomic nervous system. When compared with the resting value, it was found that normal subjects had a decrease in cardiac output during the immediate post-Valsalva recovery period, while patients with mitral stenosis had an increased output following the same stress. Three patients with alterations of the autonomic nervous system had a variable response. Changes in total peripheral vascular resistance usually were directionally opposite to changes in the cardiac output. The difficulties of attaching clinical significance to a patient's response to the Valsalva maneuver are considered.

RECENT reports suggest that patients with cardiovascular abnormalities, especially mitral stenosis, may respond differently, when compared with normal subjects, to the stress of a Valsalva maneuver[1-4] (a forced expiration with a closed glottis, after a full inspiration). It has been reported that the absence of bradycardia following the Valsalva maneuver may serve as an index for the degree of mitral stenosis.[1] It has also been observed that, unlike normal subjects, patients with mitral stenosis can maintain their systolic blood pressure equal to the resting level during the forced expiratory phase of the Valsalva maneuver when performed under effective autonomic blockade.[4]

Early observations on the altered circulatory dynamics produced by the Valsalva maneuver have been adequately reviewed[5-7]; however, few actual measurements of the cardiac output and peripheral resistance during and following this maneuver have been reported. Such measurements were made in this study in normal subjects, patients with mitral stenosis, and patients with alterations of the autonomic nervous system.

## Materials and Methods

Nine patients with normal sinus rhythm and stenosis of the mitral valve were studied by the technic of cardiac catheterization.[8] None of these patients had clinically significant involvement of other valves. Pulmonary "capillary" pressure[9] was recorded at rest and at the end of a three-minute period of leg exercise in all but one patient (WG). With the tip of the catheter in the pulmonary artery, a resting cardiac output, usually in duplicate, was measured, utilizing the direct Fick principle. (The Fick principle is routinely used in this laboratory in diagnostic catheterizations to determine the cardiac output.) The resting cardiac output was then measured by the T-1824 dye-dilution method.[10] It has been shown[11] that, allowing for the level of the cardiac output, there is no distinct difference in the contour of dye curves obtained from patients with mitral disease and normal subjects.

The cardiac output was then determined by the dye-dilution method during the recovery period immediately following a Valsalva strain which was maintained with an intraoral pressure of 40 to 50 mm. Hg for 22 to 30 seconds. Duplicate cardiac outputs were determined during successive post-

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Valsalva periods in four patients. The dye was introduced into the catheter, the tip of which was in the pulmonary artery, one second after release of the increased intraoral pressure and the systemic arterial pressure was recorded by an indwelling needle simultaneously with the determination of the cardiac outputs in all but two patients (MB and EB). In these two patients the arterial pressure was recorded under apparently the same conditions before or after the output determination.

The cardiac output was also determined by the dye-dilution technic during the period of sustained increased intrathoracic pressure in one of the above (MB) and two additional patients with mitral stenosis. In this phase of the study the dye was introduced into the catheter, the tip being in the pulmonary artery, two seconds after commencing the strain of a Valsalva maneuver.

Similar studies, with the following modifications, were carried out on eight normal subjects and three patients with alterations of the autonomic nervous system. In these 11 subjects, the catheter was passed only to the superior vena cava and cardiac outputs were determined only by the dye-dilution method. The increased intraoral pressure (40 to 50 mm. Hg) was maintained somewhat longer (average 34 seconds, range 25 to 73 seconds) in this group than by the patients with mitral stenosis.

The arterial pressure and pulse rate changes produced by the Valsalva maneuver were recorded by an indwelling arterial needle over 300 times in a heterogeneous group of 80 subjects. These records were analyzed in the four phases suggested by Hamilton[12]: phase 1, the initial rise of blood pressure following the onset of increased intrathoracic pressure; phase 2, the period of sustained strain; phase 3, the period of release of the intrathoracic pressure; phase 4, the recovery period (fig. 1). All studies were done with the subject in the recumbent position.

Oxygen consumption was measured by a Pauling oxygen analyzer. Blood samples were analyzed for oxygen content by the method of Hickam and Frayser.[13] The optical density of the dye samples was read against a serum blank on a Coleman Junior spectrophotometer at a wave length of 620 mu.[10] At least four or more points were obtained for plotting the downward slope of the post-Valsalva dye-dilution curves in all subjects.

Arterial and venous pressures were measured by a Sanborn electromanometer or a suitable Statham strain gage and recorded on a four-channel direct-writing Sanborn polyoscillograph.

The area of the mitral valve was calculated by the formula of Gorlin.[14] Total peripheral resistance was calculated:

$$\frac{\text{Mean arterial B.P.} - 0}{\text{Cardiac output cc./sec}} \times 1332 \text{ dynes seconds cm.}^{-5}$$

The arterial pressure for this determination was measured at the mean circulation time obtained from the dye-dilution curve. The mean arterial pressure was determined by the addition of the diastolic pressure and one-third the pulse pressure. The vasopressor response to the Valsalva maneuver was graded 0 to 4 by the method of Wilkins.[15]

## Observations and Results

The values for the cardiac index and total peripheral resistance are integrated determinations. This is particularly true during the recovery phase following the Valsalva maneuver when the pulse rate and blood pressure varied from stroke to stroke. The arterial pressure used for calculating the total peripheral resistance was the pressure at the mean circulation time of the dye-dilution curve despite the fact that the peak overshoot of blood pressure might have occurred some seconds earlier. The determination of total peripheral resistance, therefore, does not reflect instantaneous changes in resistance occurring immediately after release of the strain.

*Normal Subjects.* Primary attention in this study was focused on phase 4 of the Valsalva maneuver (fig. 1), which was compared with the previous resting state. This phase occurred after the release of the strain when in most instances the systolic and diastolic pressure rose rapidly, the former more than the latter, so that both the mean arterial and pulse pressures were elevated above resting levels. The maximal rise in systolic pressure usually, but not invariably, occurred within three to four seconds. The magnitude of the vasopressor response did not appear related to the duration of the strain, provided it exceeded seven seconds, or the magnitude of the increase of the intrathoracic pressure, provided it exceeded 30 mm. Hg. The vasopressor responses in the normal subjects are recorded in table 1. Slight or no vasopressor response was also observed in a number of other subjects with no obvious cardiovascular abnormality who were not studied in detail. The response of these subjects was similar to that reported by other investigators.[4]

The rise in systolic pressure was usually followed within 15 seconds or less by a brady-

TABLE 1.—*Physiologic Data of Normal Subjects, Patients with Mitral Stenosis and Alterations of the Autonomic Nervous System at Rest and during the Post-Valsalva Recovery Period*

| Subject | Resting | | | | Post-Valsalva Recovery Period | | | | | | | Per Cent Change from Resting | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cardiac Index* L./min./M.² | Pulse Rate/min.†a | Mean Arterial Press. mm. Hg‡ | Total Peripheral Resistance dynes/sec./cm.⁻⁵ | Cardiac Index* L./min./M.² | Pulse Rate/min.†b | Mean Arterial Press. mm. Hg‡ | Total Peripheral Resistance dynes/sec./cm.⁻⁵ | Mean Circulation Time sec. | Mean Arterial Pressure at Overshoot mm. H | Vasopressor Response§ | Cardiac Index | Pulse Rate | Total Peripheral Resistance |
| *Normal Subjects* | | | | | | | | | | | | | | |
| SL | 3.5 | 62 | 87 | 965 | 3.6 | 62 | 93 | 970 | 12.7 | 99 | 2 | +3 | 0 | +1 |
| TK | 4.0 | 85 | 79 | 860 | 4.3 | 69 | 100 | 1010 | 8.0 | 112 | 4 | +8 | −19 | +17 |
| FC | 4.2 | 79 | 83 | 745 | 3.1 | 68 | 128 | 1570 | 10.9 | 125 | 4 | −26 | −14 | +111 |
| JP | 3.9 | 68 | 65 | 650 | 3.0 | 54 | 70 | 895 | 14.3 | 100 | 4 | −23 | −21 | +38 |
| JB | 3.5 | 80 | 101 | 1235 | 2.8 | 70 | 129 | 2000 | 17.5 | 145 | 4 | −20 | −13 | +62 |
| MS | 4.1 | 68 | 81 | 860 | 3.1 | 63 | 95 | 1320 | 14.0 | 101 | 1 | −24 | −7 | +53 |
| WW‖ | 3.8 | 63 | 93 | 940 | 2.5 | 62 | 99 | 1500 | 35.3 | 108 | 2 | −34 | −1 | +60 |
| JR | 3.8 | 80 | 87 | 1025 | 3.8 | 70 | 95 | 1120 | 14.0 | 111 | 4 | 0 | −13 | +9 |
| | | 87 | | | 4.0 | 60 | 87 | 985 | 13.1 | 106 | 1 | +5 | −31 | −4 |
| Aver.... | 3.9 | 75 | 85 | 910 | 3.4 | 64 | 100 | 1263 | 15.5 | 112 | | −12 | −13 | +38 |
| *Patients with Mitral Stenosis* | | | | | | | | | | | | | | |
| JM | 2.6 | 97 | 63 | 1275 | 3.5 | 113 | 69 | 1020 | 9.0 | 69 | 0 | +35 | +16 | −20 |
| | | 103 | | | 3.5 | 106 | 68 | 1025 | 9.3 | 70 | 2 | +35 | +3 | −20 |
| CP | 2.1 | 104 | 70 | 1520 | 2.5 | 86 | 86 | 1330 | 23.0 | 95 | 1 | +19 | −17 | −13 |
| CS | 3.1 | 81 | 65 | 1235 | 2.9 | 72 | 88 | 1770 | 11.4 | 89 | 3 | −6 | −11 | +43 |
| JC | 2.6 | 80 | 78 | 1300 | 2.0 | 73 | 96 | 2080 | 14.5 | 95 | 2 | −23 | −9 | +60 |
| | | 83 | | | 2.1 | 100 | 102 | 2100 | 14.4 | 95 | 2 | −19 | +21 | +62 |
| MB | 1.6 | 68 | 67 | 2330 | 2.3 | 84 | 81 | 1930 | 15.0 | 90 | 3 | +44 | +24 | −17 |
| WM | 1.8 | 64 | 59 | 1400 | 2.2 | 64 | 70 | 1360 | 17.9 | 73 | 2 | +22 | 0 | −3 |
| | | 64 | | | 2.1 | 62 | 70 | 1385 | 20.1 | 73 | 2 | +17 | −2 | −1 |
| WG | 2.3 | 78 | 77 | 1465 | 2.6 | 60 | 97 | 1610 | 16.0 | 106 | 4 | +13 | −23 | +10 |
| | | 77 | | | 2.3 | 65 | 94 | 1840 | 15.7 | 103 | 4 | 0 | −16 | +26 |
| AF | 2.9 | 92 | 69 | 985 | 3.7 | 113 | 98 | 1315 | 12.2 | 104 | 4 | +28 | +23 | +34 |
| EB | 1.9 | 72 | 68 | 1760 | 1.7 | 62 | 85 | 2370 | 18.2 | 95 | 4 | −11 | −14 | +35 |
| Aver.... | 2.3 | 82 | 68 | 1474 | 2.6 | 82 | 85 | 1626 | 15.1 | 89 | | +12 | −4 | +15 |
| *Patients with Alterations of the Autonomic Nervous System* | | | | | | | | | | | | | | |
| AM | 2.1 | 82 | 133 | 3065 | 3.9 | 142 | 112 | 1400 | 8.8 | | 0 | +45 | +74 | −54 |
| MCB | 3.6 | 83 | 73 | 810 | 2.9 | 83 | 49 | 695 | 16.8 | | 0 | −19 | 0 | −14 |
| | | | | | 2.4 | 83 | 49 | 825 | 15.9 | | 0 | −33 | 0 | +2 |
| VB | 3.6 | 70 | 85 | 1305 | 4.2 | 98 | 86 | 1160 | 7.5 | | 0 | +17 | +40 | −10 |
| Aver.... | 3.1 | 78 | 97 | 1727 | 3.4 | 102 | 74 | 1020 | 12.3 | | | +3 | +29 | −19 |

* Determined by the dye-dilution method.

† Six-second period: (a) Prior to the Valsalva maneuver. (b) Maximal period of bradycardia within 15 seconds of the maximal rise of systolic pressure following the release of the strain.

‡ Determined at the mean circulation time of the dye-dilution curve.

§ According to the method of Wilkins.[15]

‖ Only normal subject not a medical student.

cardia. To be considered significant the pulse rate had to be reduced 10 per cent of the resting rate for a six-second interval within 15 seconds of maximal systolic overshoot. No bradycardia was observed without at least a grade 1 vasopressor response. However, it was not uncommon to observe grade 4 vasopressor responses without a significant bradycardia; nor

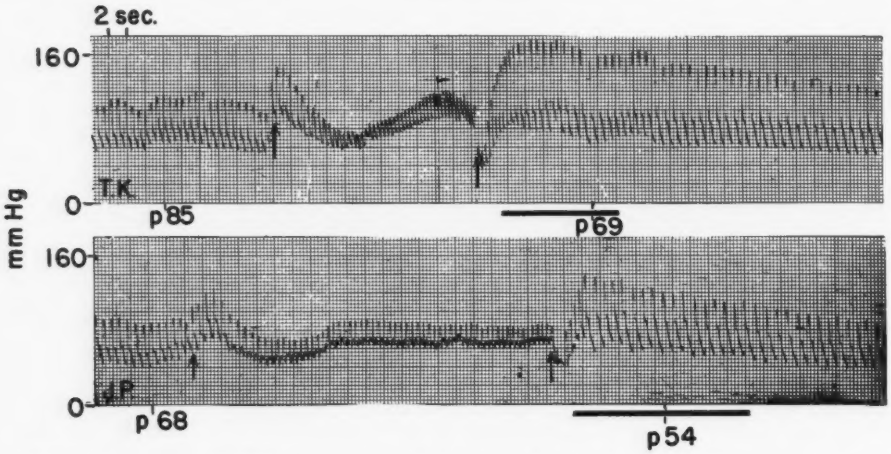


FIG. 1. Response to the Valsalva maneuver in two normal medical students. The arrows indicate the onset and release of the strain. The response to the Valsalva maneuver was divided into four phases.[12] Phase 1 indicates the initial blood pressure rise and phase 2 the continuation of the strain. Phase 3 indicates the precipitous fall of the arterial pressure upon the release of the strain, and phase 4 denotes the recovery period. Cardiac outputs were determined simultaneously while these tracings were recorded. The heavy black line at the base of the tracing indicates the period over which the dye-dilution curve was obtained in this and subsequent figures. In TK, the cardiac output increased 8 per cent over the resting value while in JP the output decreased 23 per cent. In all figures "P" indicates the pulse rate over a six-second period.

was it uncommon to observe marked bradycardia following grade 1 or 2 vasopressor responses.

Table 1 shows the cardiac index and total peripheral resistance as determined in eight normal male subjects during the resting and immediate post-Valsalva recovery period. When compared with the resting cardiac index, the index during the immediate post-Valsalva recovery period was decreased an average of 12 per cent (range +8 to −34 per cent). In no subject was there a significant increase of the cardiac output following the Valsalva. No correlation between the degree of the vasopressor response, the magnitude of the increased intrathoracic pressure or the duration of the strain and the resultant change of cardiac output was apparent. In five of the eight subjects in whom the cardiac index was decreased 20 per cent or more following the Valsalva maneuver, the total peripheral resistance was increased 38 per cent or more (table 1).

*Patients with Mitral Stenosis.* Pertinent data on the circulatory dynamics of the patients with mitral stenosis are contained in table 2. Eight of the 11 patients had calculated valve areas of 1.1 sq. cm. or less, and all but three of the group subsequently had a mitral valvotomy.* The valve areas estimated at surgery are also recorded in table 2.

During phase 4 of the Valsalva maneuver, patients with mitral stenosis, usually had an increased systolic and diastolic pressure when compared with the resting level. The former increased more than the latter so that there was an increase in both the pulse and mean pressure. However, as has been previously observed,[3] the patients with mitral stenosis attained the maximal rise of systolic pressure somewhat later than did normal subjects (figs. 1 and 2). Whereas normal subjects had the maximal vasopressor response within four seconds following the release of the strain, patients with mitral stenosis usually required six to eight seconds to reach the peak of the vasopressor response. The vasopressor response of these patients is recorded in table 1.

* Performed by W. C. Sealy, M.D., and J. P. Collins, M.D.

Patients with mitral stenosis frequently also had a bradycardia following the maximal rise of systolic pressure. Seven of the 11 cases in this study had a pulse rate during phase 4 of 10 to 23 per cent less than the resting level in one or all of a number of Valsalva maneuvers. This slowing of the pulse was frequently of short duration (at least six seconds) and, like the maximal rise in systolic pressure, did not always occur as promptly as did the bradycardia in normal subjects. However, to be considered significant, the bradycardia had to occur within 15 seconds of the maximal rise of systolic pressure. This bradycardia was frequently preceded by a relative tachycardia. It should be noted that the maximal vasopressor and bradycardic response for a given patient to a Valsalva maneuver is not necessarily recorded in table 1. The recorded vasopressor responses accompanied the reported cardiac output. A significant bradycardia following the Valsalva maneuver was also observed in three additional patients subjected to mitral valvotomy.

Table 1 shows the cardiac index and total peripheral resistance measured during the recovery phase of the Valsalva maneuver in nine patients with mitral stenosis. The cardiac index during this recovery period, when compared with the resting value, increased an average of 12 per cent (range +35 to −23 per cent). In only one patient was the index during the recovery phase considerably decreased below the resting level (JC, −19 and −23 per cent). Of five patients who, following the Valsalva maneuver, had a cardiac output greater than 16 per cent of the resting output, only one (AF), had a significant increase of the total peripheral resistance (+34 per cent). The total peripheral vascular resistance was unchanged or increased in the other four patients who had no change or a decrease in the cardiac output during this period.

The cardiac output was also measured during the period of increased intrathoracic pressure in three patients with mitral stenosis. During this period it was decreased 25, 52 and 65 per cent, respectively.

*Patients with Autonomic Nervous System Alterations.* The etiologic mechanism of the defect in the autonomic nervous system varied in these three patients. AM had persistent symptoms of postural hypotension following a lumbar sympathectomy four years prior to this study. MCB had diabetes mellitus and associated postural hypotension with a fixed pulse rate. Both of these patients were incapacitated by their postural symptoms. VB had had a lumbodorsal sympathectomy for severe essential hypertension eight weeks prior to this study. She had no significant postural symptoms.

During phase 4 of the Valsalva maneuver these patients did not have an overshoot of

TABLE 2.—*Physiologic Data of Patients with Mitral Stenosis*

| Subject | State | Pulse Rate | mm. Hg | | A-V Difference vols. per cent | Cardiac Index‡ L./min./M.² | Stroke Volume cc./beat | Mitral Valve Area cm.² | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Pulmonary "Capillary" (mean) | Pulmonary Artery (mean) | | | | Calculated§ | At Surgery |
| JM | R | 84 | 18 | 18 | 3.9 | 3.1 | 56 | 1.1 | 0.6 |
| | E | | 32 | | | | | | |
| CP | R | 98 | 28 | 72 | 6.8 | 2.5 | 53 | 1.0 | 0.7 |
| | E | | 28 | 87 | | | | | |
| CS | R | 82 | 26 | 42 | 6.1 | 3.3 | 55 | 0.8 | 0.7 |
| | E | | 44 | | | | | | |
| JC | R | 78 | 22 | 41 | 4.6 | 2.7 | 64 | 1.0 | 0.4 |
| | E | 102 | 27 | 92 | 11.5 | 2.8 | 50 | | |
| MB | R | 63 | 17 | 22 | 5.6 | 2.3 | 52 | 0.7 | * |
| | E | | 33 | | | | | | |
| WM | R | 54 | 20 | 31 | 7.4 | 1.9 | 65 | 0.7 | 0.7 |
| | E | | 30 | | | | | | |
| WG | R | 75 | | 35 | 4.6 | 2.6 | 64 | | 0.7 |
| | E | 107 | | 81 | 7.7 | 3.5 | 60 | | |
| AF | R | 85 | 27 | 31 | 3.9 | 3.5 | 66 | | |
| | E | 100 | 35 | | 7.4 | 3.5 | 59 | 1.0 | † |
| EB | R | 72 | 7 | 11 | 5.4 | 2.0 | 47 | | |
| | E | | 17 | | | | | 2.6 | † |
| JS | R | 73 | | 26 | 7.2 | | | | † |
| | E | 97 | | 60 | | | | | |
| FW | R | 83 | 24 | 35 | 6.0 | 1.6 | 35 | 0.8 | 1.0 |
| | E | 100 | 37 | | | | | | |

* Surgeon could not estimate because of calcification.

† Not operated.

‡ Fick principle.

§ Determined by the Gorlin formula.[14]

R. Resting. E. Exercise.

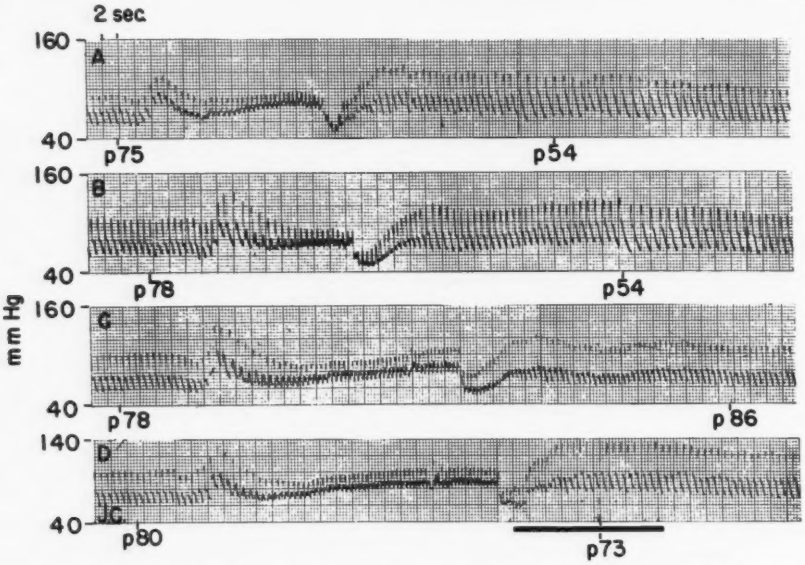


FIG. 2. Four tracings recorded from the same patient with mitral stenosis under similar resting conditions. The mitral valve in this patient was subsequently estimated at operation to be 0.4 sq. cm. The presence of a bradycardia in phase 4 does not appear to be related to the duration of the strain. Contrary to most patients with mitral stenosis in this series, the cardiac output was 23 per cent below the resting level. Note the delay in reaching the maximal rise in systolic pressure following the release of the strain, as compared with normal subjects (fig. 1).

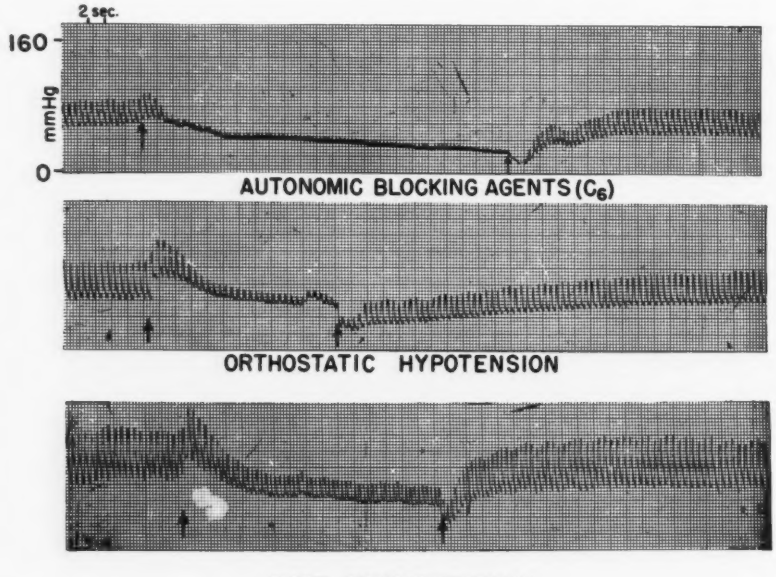


FIG. 3. The absence of the arterial overshoot following the release of the strain and a prolonged recovery period is associated with alterations of the autonomic nervous system.

systolic or diastolic pressure (fig. 3). The time required for the systemic blood pressure to return to the previous resting levels was prolonged. Both the systolic and diastolic pressures were below the resting level for three minutes following the release of the strain in one patient (AM). MCB had a fixed pulse rate which persisted during the recovery period. The other two patients had an increase in pulse rate during this period.

Table 1 shows the changes in the cardiac output and total peripheral resistance measured during the recovery phase of the Valsalva maneuver. Two patients had increased outputs during this period of 17 and 45 per cent, respectively. The patient with a fixed pulse rate (MCB) had a decreased output on two occasions of 19 and 33 per cent. An increase of total peripheral resistance during the recovery period was not observed in any patient.

*Comment.* The duration of phase 1 (fig. 1), indicating the initial maximal rise of the systolic and diastolic pressure in response to the increase of the intrathoracic pressure, varied from 1 to 5 pulse beats. The rapidity of the onset of this increase in arterial pressure was directly related to the speed of attaining the greatest rise of intrathoracic pressure. A sudden increase in intrathoracic pressure, as in a cough which was sustained, caused the maximal rise in both the systolic and diastolic pressure within one beat. If the intrathoracic pressure was increased slowly, phase 1 was more prolonged. This response was uniformly observed in all types of subjects.

## Discussion

It has been generally accepted that when the intrathoracic pressure is increased by straining against the closed glottis or blowing against a column of mercury, the venous return to the heart is slowed and the cardiac output is considerably reduced.[1, 7, 12, 16] An obstruction to venous return produced by the Valsalva maneuver at the level of the first rib has recently been conclusively demonstrated[17] by venograms.

Using radiographic technics, Natvig[18] concluded that the volume of the heart decreased approximately 200 cc. during the strain. Utilizing the dye-dilution technic, three patients with mitral stenosis had an average reduction in cardiac output of 47 per cent (table 3). A similar reduction by this technic was observed in patients without mitral stenosis.[19]

Following the release of the strain, it has been assumed[1, 12, 21] that the blood previously dammed in the venous system was immediately presented to the right ventricle and resulted in a rapid increase in cardiac output. Hamilton[12] stated that the blood dammed back in the extrathoracic reservoirs made its way through the lesser circulation and produced a maximal effect on the arterial pressure in four seconds. Few actual measurements of the cardiac output during this recovery period are available in the literature. Otis and co-workers[20] reported observations on two subjects in whom the stroke volume, measured by the ballistocardiograph, decreased following the release of the strain, but the pulse rate increased so that the cardiac output increased 119 and 158 per cent above the resting output. Kay and associates,[21] utilizing electrokymographic technics, observed that 8 of 10 healthy subjects in the sitting position (the subjects in the present study were recumbent) had increased aortic pulsations within four beats after the release of the strain. These increased pulsations were interpreted as indicating an increase in cardiac output. Venhofen,[22] using the pulse velocity method of Broemser and Ranke, reported the cardiac output in three of four patients to be decreased during the Valsalva recovery period 31, 41 and 31 per cent, respectively, when compared with resting values. Wilkins and Culbertson[15] found that the cardiac output measured by the ballistocardiograph, when compared with the resting output, was decreased in the period immediately following termination of the Valsalva maneuver in patients with hypertensive vascular disease.

Figure 4 shows that the normal subjects in this study had a decrease or no change in cardiac output following a period of increased intrathoracic pressure when compared with the resting value; the patients with mitral stenosis, however, with one exception (JC),

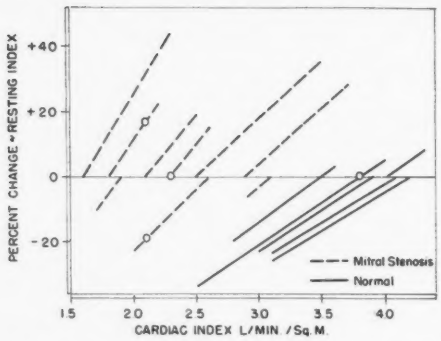


FIG. 4. Change in cardiac index following the Valsalva maneuver. Subjects with low resting cardiac indexes tend to have an increased cardiac output following the Valsalva maneuver while those with high or normal resting indexes tend to have a decreased output following the same stress. The small circles indicate duplicate determinations of the cardiac index.

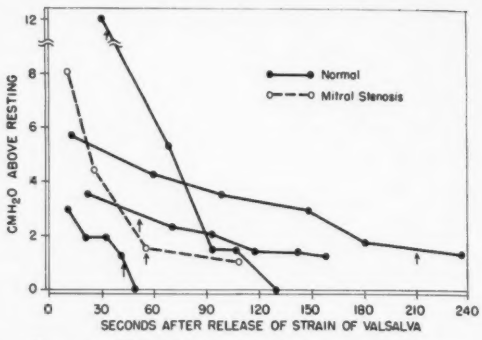


FIG. 5. Elevation of central venous pressure following Valsalva maneuver. The arrows indicate the return of the arterial pressure to normal following the Valsalva maneuver.

had an increase or no change in cardiac output in response to the same stimuli.

Insufficient cardiac filling was not the cause of the decreased cardiac output in normal subjects during phase 4 of the Valsalva maneuver, for, as seen in figure 5, the central venous pressure remained elevated for a considerable time after the release of the strain. A decrease in cardiac output with an elevated right auricular pressure has previously been observed with other alterations of hemodynamic equilibrium.[23]

A bradycardia was not observed in any subject in this study without an associated increase in arterial pressure, although a marked increase in arterial pressure in phase 4 was not always accompanied by bradycardia. The bradycardia following the release of the increased intrathoracic pressure is similar to that observed following occlusion of an arteriovenous fistula.[24] In the latter condition, the slowing of the pulse is also associated with a rise in arterial pressure. The bradycardia following occlusion of an arteriovenous fistula may be abolished by atropine, despite the fact that the increase in arterial pressure is greater than that observed before administration of the drug. Atropine also blocks the bradycardia following the Valsalva maneuver despite an even greater overshoot of arterial pressure than observed without the medication.[2] As the cardiac output may be reduced in normal subjects in the immediate post-Valsalva recovery period, it is of interest that following the occlusion of an arteriovenous fistula, in subjects without evidence of heart failure, there is an immediate decrease in the cardiac output due to a decreased stroke volume.[24] Atropine does not prevent this decreased stroke volume. It was thought that the decrease in stroke volume was due to variations in diastolic relaxation of the ventricle or to variations in the completeness of systolic emptying.

Examination of table 1 shows that in general, when compared with resting values, the subjects who had an increase of the total peripheral resistance during the post-Valsalva recovery period, usually had a decrease in cardiac output. Those who had a decrease in total peripheral resistance during this period had an increase in cardiac output. All subjects, however, usually had an increase in arterial pressure during this period.

The relationship between the cardiac output and peripheral vascular resistance in determining the degree of response to the Valsalva is further demonstrated by three patients with alterations of the autonomic nervous system. None had an increase in peripheral resistance in response to the stress of a Valsalva maneuver. Two of these patients had an increase in cardiac output and pulse rate during this period (table 1). However, despite a 45 per cent increase in cardiac output, the arterial pressure in one patient (AM) was below the

resting level. The third patient (MCB) had a decrease in cardiac output; however, he was further complicated by having a fixed pulse rate which did not vary during any phase of the Valsalva maneuver or in response to other stimuli which would usually alter the heart rate. His arterial pressure was considerably below the resting value.

Goldberg, Elisberg, and Katz[1] have stated that patients with significant mitral stenosis do not have an overshoot of arterial pressure nor bradycardia following the release of a Valsalva maneuver. However, in this study and that of Greene and Bunnell,[4] a significant overshoot of arterial pressure and associated bradycardia was frequently observed in such patients. Goldberg and associates[1] felt that the overshoot of pressure in normal subjects was due to the rapid increase of cardiac output following the release of the strain and that the stenosed mitral valve prevented such an increase. The present study does not support such an opinion.

It was indeed surprising to observe that the cardiac output in patients with significant mitral stenosis, following a period of increased intrathoracic pressure, not only equalled but frequently exceeded the resting output. Flow through a stenosed mitral valve is dependent on the pressure gradient across that valve. An increase in flow through the valve may be produced by an increase of left auricular pressure, or a decrease in left ventricular end diastolic pressure. Goldberg and associates[1] pointed out that patients with mitral stenosis reach the maximal rise of systolic overshoot following a Valsalva procedure slower than normal subjects. Such a delay may reflect a period in which the left auricular pressure is increasing. The increased left auricular pressure could thus increase the pressure gradient across the stenosed mitral valve and result in an increased cardiac output.

Further discussion as to the reason that patients with mitral stenosis frequently had an increased output following the stress of a Valsalva maneuver while normal subjects tended to have a decreased output would be purely speculative. The data obtained in this study simply permits one to state that following the Valsalva maneuver, the response observed in the arterial tracing is due to an interplay of cardiac output, total peripheral vascular resistance, and other at present poorly understood hemodynamic mechanisms. Alteration in venous tone has been observed in the isolated vein segment during this maneuver.[25] Some subjects have been observed to have an increase over the resting forearm blood flow, as measured by the plethysmograph, when the cardiac output was actually decreased.[26] Greene and Bunnell[4] have observed with tetraethylammonium chloride (TEAC) a difference between normal subjects and patients with mitral stenosis during phase 2 of the maneuver. These and other variables may alter in importance from patient to patient and in the same patient from time to time.

The complexity and multiplicity of changes occurring during and following the period of increased intrathoracic pressure are apparent. Without simultaneous precise measurements of these variables, an interpretation, especially a clinical interpretation, of the phenomena producing the changes observed in an arterial tracing during and following a Valsalva maneuver should be made with caution.

## Summary

1. Circulatory changes produced by the Valsalva maneuver have been investigated in normal subjects, in patients with mitral stenosis, and in patients with alterations of the autonomic nervous system.

2. Compared with resting values, the cardiac output as measured by the dye-dilution technic tended to be decreased during the post-Valsalva recovery period in normal subjects but increased in patients with mitral stenosis. Two patients with autonomic nervous system alterations had increased outputs and one had a decreased output during this period.

3. The total peripheral vascular resistance tended to change inversely to the cardiac output during this recovery period.

4. It is suggested that caution should be exercised in attaching clinical significance to the response to a Valsalva maneuver.

## Sumario Español

1. Los cambios circulatorios producidos por la maniobra de Valsalva han sido investigados

en sujetos normales, en pacientes con estenosis mitral, y en pacientes con alteraciones del sistema autonómico nervioso.

2. Comparado con los valores durante el reposo, la producción cardíaca medida por la técnica de dilución de tinte tendió a disminuir durante el período de recobro post-Valsalva en sujetos normales pero aumento en los pacientes con estenosis mitral. Dos pacientes con alteraciones del sistema nervioso autonómico tuvieron producciones aumentadas y uno tuvo una producción disminuida durante este período.

3. La resistencia perífero vascular total tendió a cambiar inversamente con la producción cardíaca durante el período de recobro.

4. Se sugiere que se ejerza cautela en asignar significado clínico a la respuesta a la maniobra de Valsalva.

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# Intravenous Hexamethonium Sensitivity and Responses to Oral Treatment

*By* D. M. Green, M.D., and Eugene J. Ellis, M.D.

This study represents an effort to distinguish between neurogenic and humoral vasoconstrictive factors in a representative group of hypertensive patients by the response to hexamethonium ganglionic blockade. The correlation between intravenous hexamethonium sensitivity and subsequent treatment response was also determined.

ONE of the most difficult problems in essential hypertension is to select the treatment most apt to benefit the individual patient. Many present-day therapies are believed to act by blocking or depressing some part of the nervous system in the patient with excessive neurogenic vasoconstriction. The effects of cold,[1] sleep and barbiturate administration[2] and spinal anesthesia[3] have been used to select this type of patient for treatment. None of these measures has been conspicuously successful,[4] perhaps because their action is not confined to the neurogenic pressor mechanism or, conversely, is incomplete.

The effect of hexamethonium chloride appears to be limited to a temporary blockade of sympathetic and parasympathetic ganglia.[5] The drug can be given intravenously at any desired concentration and rate. For these reasons, we have used an intravenous hexamethonium test to determine whether patients with excessive neurogenic vasoconstriction could be singled out by their response to autonomic blockade; and, as a corollary, whether the existence of significant non-neurogenic vasoconstriction could be demonstrated by the failure of the blood pressure to fall materially after maximum tolerated doses of hexamethonium. We have also attempted to determine whether the results of oral hexamethonium treatment could be anticipated from the intravenous response.

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This study is part of a project made possible by current grants from the Los Angeles County Heart Association and the United States Public Health Service.

## Methods and Materials

The subjects were 23 patients with essential hypertension, ranging in age from 26 to 72 years. None showed evidences of coronary insufficiency or congestive failure at the time of study. The known duration of the disease ranged from 6 months to 30 years. The status of each patient was evaluated by a complete history and physical examination, x-ray study for heart size, electrocardiogram, urinary concentration test and blood nonprotein nitrogen determination. Funduscopic findings, heart size, and electrocardiographic patterns were graded from 1 to 4. The results of these evaluations indicated that the subject group represented a wide range of hypertensive disease (table 1).

The intravenous hexamethonium test was performed as follows: The height and weight were measured and the surface area calculated. The blood pressure was then determined with a mercury sphygmomanometer at one- to two-minute intervals with the patient sitting. After the pressure had stabilized, a 2 per cent solution of hexamethonium chloride was injected into an antecubital vein.* The drug was administered in increments of 1 to 10 mg. every one to three minutes, depending on the patient's response. Injection of the drug was stopped after the systolic pressure had fallen half-way or more to normal (150 mm. Hg).†

Following the test, the patient was placed supine until the blood pressure had returned to hypertensive levels. The amount of drug needed to produce the standard fall in pressure was used as the index of sensitivity toward intravenous hexamethonium.

Twenty-one of these subjects were treated with oral hexamethonium chloride for periods of three

* We are indebted to Dr. Fredrick F. Yonkman of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for the special preparation of the hexamethonium chloride solution.

† This end-point was chosen because the blood pressure continues to drop for a variable period after intravenous administration is discontinued. As a consequence, irreversible shock from overdosage is a potential hazard.

TABLE 1.—*The Responses of 23 Patients with Essential Hypertension to Intravenous and Oral Hexamethonium in Relation to Their Clinical Status*

| Subject, Initials | Sex (M) | Sex (F) | Age (Yrs.) | Surface Area ($m.^2$) | Duration (Yrs.) | Fundi* | Heart Size* | ECG* | Maximum Urinary Conc. (S.G.) | NPN (mg.%) | I.V. HXM Dose (mg./$M.^2$) | Pretest BP (mm. Hg) S | Pretest BP (mm. Hg) D | Pretest BP (mm. Hg) S/D | Posttest BP (mm. Hg) S | Posttest BP (mm. Hg) D | Posttest BP (mm. Hg) S/D | Pulse (beats/min.) Pre- | Pulse (beats/min.) Post- | Oral HXM dose at Minimum BP (Gm./day) | Minimum Treatment BP (mm. Hg) S | Minimum Treatment BP (mm. Hg) D | Minimum Treatment BP (mm. Hg) M | Minimum Treatment BP (mm. Hg) S/D | Time of Minimum BP (Days of treatment) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Sensitive Group* | | | | | | | | | | | | | | | | | | | | | | | | | |
| A. Y. | | x | 72 | 1.39 | 6.0 | 3 | 1 | 1 | 1.013 | 58 | 1.4 | 260 | 115 | 2.26 | 140 | 60 | 2.34 | 72 | 72 | 2.0 | 120 | 64 | 92 | 1.88 | 21 |
| F. M. | x | | 38 | 1.85 | 3.0 | 2 | 2 | 1 | 1.020 | 23 | 1.6 | 231 | 151 | 1.53 | 94 | 70 | 1.34 | 112 | 96 | 3.0 | 138 | 99 | 119 | 1.40 | 28 |
| M. P. | | x | 61 | 1.80 | 1.0 | 2 | 2 | 3 | 1.021 | 34 | 1.7 | 203 | 122 | 1.66 | 124 | 70 | 1.75 | 64 | 66 | 2.0 | 162 | 98 | 130 | 1.65 | 14 |
| A. L. | | x | 43 | 2.01 | 12.0 | 1.5 | 1 | 3 | 1.024 | 47 | 2.0 | 201 | 136 | 1.48 | 120 | 100 | 1.20 | 108 | 108 | 3.0 | 142 | 110 | 126 | 1.29 | 21 |
| L. P. | | x | 65 | 1.49 | 1.0 | 1 | 1 | 2 | 1.017 | 32 | 2.1 | 175 | 113 | 1.55 | 115 | 90 | 1.28 | 72 | 96 | 2.0 | 142 | 100 | 121 | 1.42 | 35 |
| E. A. | x | | 53 | 2.13 | 0.5 | 1 | 1 | 1 | 1.020 | 36 | 2.3 | 183 | 110 | 1.66 | 125 | 120 | 1.04 | 96 | 96 | 0.5 | 120 | 92 | 106 | 1.33 | 21 |
| E. H. | | x | 65 | 1.64 | 19.0 | 2.5 | 1 | 2 | 1.018 | 28 | 2.4 | 198 | 125 | 1.58 | 140 | 95 | 1.48 | 76 | 96 | 2.0 | 145 | 88 | 117 | 1.65 | 70 |
| R. D. | x | | 48 | 1.69 | 5.0 | 2 | 3 | 3 | 1.015 | 46 | 2.4 | 207 | 123 | 1.68 | 158 | 118 | 1.34 | 64 | 76 | 3.0 | 170 | 108 | 139 | 1.57 | 49 |
| L. P. | x | | 51 | 2.02 | 15.0 | 2 | 1 | 1 | 1.019 | 43 | 2.5 | 217 | 133 | 1.63 | 130 | 95 | 1.37 | 70 | 72 | 2.0 | 151 | 108 | 130 | 1.40 | 14 |
| L. S. | | x | 68 | 1.28 | 18.0 | 1 | 1 | 1 | 1.018 | 44 | 3.1 | 227 | 102 | 2.23 | 170 | 90 | 1.89 | | | 2.0 | 160 | 78 | 119 | 2.05 | 35 |
| J. J. | x | | 41 | 1.94 | 8.0 | 3 | 2 | 3 | 1.015 | 64 | 3.1 | 178 | 136 | 1.31 | 130 | 106 | 1.23 | 76 | 80 | | | | | | |
| Average..... | | | 55 | 1.75 | 8.1 | 1.9 | 1.5 | 1.9 | 1.018 | 41 | 2.2 | 207 | 124 | 1.69 | 131 | 92 | 1.48 | 81 | 86 | 2.2 | 145 | 95 | 120 | 1.56 | 31 |
| *Resistant Group* | | | | | | | | | | | | | | | | | | | | | | | | | |
| F. H. | | x | 53 | 1.50 | 18.0 | 2 | 1 | 3 | 1.012 | 45 | 4.7 | 201 | 103 | 1.95 | 160 | 100 | 1.60 | 76 | 68 | 2.0 | 173 | 95 | 134 | 1.82 | 14 |
| T. J. | | x | 40 | 1.68 | 7.0 | 2 | 2 | 3 | 1.018 | 37 | 4.8 | 230 | 140 | 1.64 | 154 | 110 | 1.40 | 80 | 84 | 2.0 | 188 | 120 | 159 | 1.57 | 63 |
| D. W. | | x | 46 | 1.59 | 21.0 | 2 | 1 | 1 | 1.017 | 28 | 5.0 | 199 | 118 | 1.69 | 144 | 102 | 1.41 | 68 | 72 | | | | | | |
| C. Mc. | | x | 63 | 1.53 | 3.0 | 2 | 2 | 2 | 1.009 | 27 | 5.2 | 231 | 97 | 2.38 | 168 | 90 | 1.87 | 80 | 84 | 3.0 | 172 | 73 | 123 | 2.36 | 35 |
| J. F. | | x | 42 | 1.45 | 1.5 | 1.5 | 1 | 1 | 1.019 | 25 | 5.5 | 170 | 106 | 1.60 | 132 | 96 | 1.38 | 103 | 136 | 0.5 | 159 | 103 | 131 | 1.54 | 7 |
| M. C. | | x | 57 | 1.72 | 12.0 | 2.5 | 2 | 2 | 1.020 | 39 | 7.0 | 226 | 121 | 1.87 | 120 | 90 | 1.33 | 60 | 72 | 1.5 | 190 | 98 | 144 | 1.94 | 14 |
| L. B. | x | | 47 | 1.68 | 30.0 | 2 | 3 | 3 | 1.020 | 39 | 7.3 | 237 | 140 | 1.69 | 190 | 130 | 1.46 | 72 | 72 | 1.0 | 194 | 110 | 152 | 1.76 | 21 |
| A. A. | | x | 58 | 1.90 | 11.0 | 2 | 3 | 2 | 1.017 | 33 | 8.4 | 224 | 141 | 1.59 | 120 | 100 | 1.20 | 72 | 80 | 1.0 | 168 | 108 | 138 | 1.56 | 7 |
| W. C. | x | | 43 | 2.04 | 3.0 | 2 | 2 | 1 | 1.024 | 28 | 10.8 | 173 | 115 | 1.50 | 114 | 88 | 1.30 | 70 | 96 | 3.0 | 171 | 117 | 144 | 1.46 | 21 |
| S. D. | x | | 43 | 1.61 | 10.0 | 2 | 1 | 3 | 1.023 | 37 | 11.4 | 238 | 134 | 1.78 | 172 | 116 | 1.48 | 96 | 108 | 1.0 | 182 | 109 | 146 | 1.67 | 10 |
| F. N. | | x | 47 | 1.60 | 20.0 | 2 | 1 | 3 | 1.030 | 21 | 15.0 | 196 | 129 | 1.52 | 140 | 110 | 1.27 | 80 | 96 | 1.0 | 189 | 122 | 156 | 1.55 | 6 |
| S. W.† | | (x) | (26) | (1.74) | (6.0) | (2) | (1) | (1) | | | (13.8) | (198) | (125) | (1.58) | (135) | (95) | (1.42) | (68) | (100) | | | | | | |
| S. W.‡ | | x | 26 | 1.74 | 6.0 | 2 | 1 | 1 | 1.020 | 30 | 23.0 | 168 | 130 | 1.29 | 130 | 100 | 1.30 | 74 | 120 | 3.0 | 169 | 115 | 142 | 1.47 | 14 |
| Average..... | | | 47 | 1.67 | 11.9 | 2.0 | 1.7 | 2.1 | 1.019 | 32 | 9.0 | 208 | 123 | 1.71 | 145 | 103 | 1.42 | 78 | 91 | 1.9 | 178 | 106 | 143 | 1.70 | 19 |
| Average both groups..... | | | 51 | 1.71 | 10.5 | 2.0 | 1.6 | 2.0 | 1.019 | 37 | 5.8 | 208 | 123 | 1.70 | 139 | 95 | 1.46 | 79 | 89 | 2.1 | 162 | 101 | 132 | 1.64 | 25 |

* Graded 1 to 4. † During pre-eclamptic episode. Values not included in averages. ‡ Six weeks after cesarean section.

weeks to six months, depending on the severity of side effects and the maintenance of a satisfactory reduction in pressure. The initial dose of 125 or 250 mg., four times daily, was increased by 125 mg. increments to a maximum (when tolerated) of 3 Gm. per day. Throughout treatment the blood pressure was measured at the same time each week in the sitting and standing positions. The lowest blood pressure reached during treatment was used as the measure of the oral therapeutic response. Usually the pressure reverted upward again, despite the continuance of the same or larger oral doses. This secondary rise was interpreted as being the result of the development of tolerance toward the hypotensive effect of hexamethonium; the rapidity with which tolerance developed was gauged by the number of treatment days required to achieve the point of minimum pressure.

## Results

The pretest blood pressure of the group averaged 208/123. Following intravenous hexamethonium administration, the group pressure fell to 139/98 (fig. 1). The ratio of systolic to diastolic pressure dropped from 1.70, pretest, to 1.45. To determine if this latter change was a specific drug effect, an additional study was made of the ratios found in 75 subjects, both normotensive and hypertensive, under basal conditions (fig. 2). The results demonstrated that the systolic-diastolic ratio was correlated with the level of systolic pressure ($r_{xy} = 0.409$; $t = 3.54$; $p < 0.0001$). The ratios observed after intravenous hexamethonium administration showed a similar correlation ($r_{xy} = 0.401$; $t = 2.01$; $p = 0.06$) and appeared to follow the pattern exhibited by individuals with normally low blood pressures.

The mean pulse rate after hexamethonium administration rose from 79 beats per minute, pretest, to 89 at the nadir of the pressure fall. In only four instances did the rate rise above 100.

Individual pressures were reduced to the desired end-point in all subjects, but the hexamethonium requirement varied from 1.4 to 23.0 mg. per square meter of body surface area. Unlike many hypotensive agents, successive increments of hexamethonium did not usually produce a proportional decline in blood pressure. Instead, little or no change in pressure (or pulse rate) ordinarily occurred until a critical level of dosage was approached. Its imminence was usually heralded by a transitory dip in pressure and by sighing. The subsequent one or two drug increments were followed by an abrupt and marked drop, which continued after the injection had been stopped. In 17 instances the pressure declined into or below the normal range, with a return to hypertensive levels 1 to 45 minutes after the

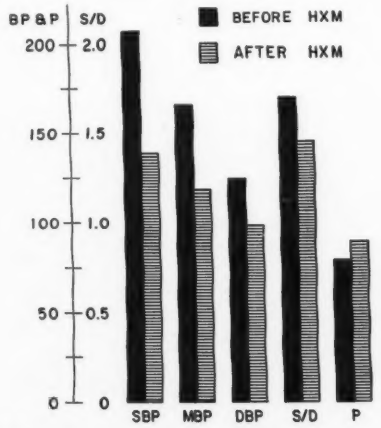


FIG. 1. Blood pressure and pulse rate in a group of 23 hypertensive subjects before and after the intravenous injection of hexamethonium chloride. *SBP* = systolic blood pressure (millimeters Hg); *MBP* = mean blood pressure (average of systolic and diastolic; millimeters Hg); *DBP* = diastolic blood pressure (millimeters Hg); *S/D* = systolic-diastolic pressure ratio; *P* = pulse rate (beats per minute).

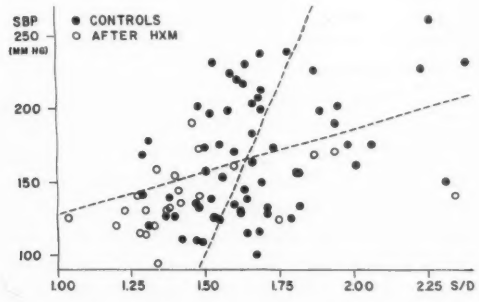


FIG. 2. Relation of systolic-diastolic pressure ratio to systolic blood pressure in 75 hypertensive and normotensive subjects under basal conditions (solid circles) as compared with 23 hypertensive subjects after intravenous hexamethonium injection (open circles). The broken lines represent the regressions from the X and Y axes in the basal group. ($r_{xy} = 0.409$; $t = 3.54$; $p < 0.0001$).

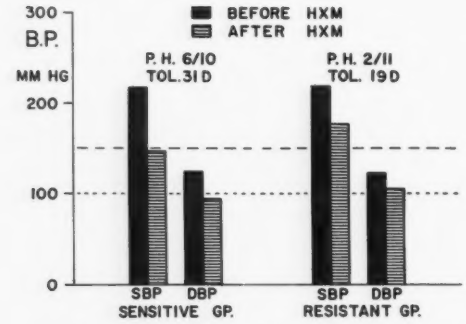


FIG. 3. The maximum results of oral hexamethonium treatment in the "sensitive" and "resistant" halves of the subject group (as classified by their response to the intravenous hexamethonium test). *SBP* = systolic blood pressure (millimeters Hg); *DBP* = diastolic blood pressure (millimeters Hg); *P.H.* = incidence of postural hypotensive reactions; *Tol.* = days of treatment required for the development of tolerance to the oral therapeutic effect.

patient had been placed in the supine position. The minimum value to which the blood pressure fell and the time required for recovery were, in general, inversely proportional to the total dose; the larger the dose needed to lower the pressure, the smaller was the tendency toward a postinjection decline into or below the normotensive range, and the more rapid was the reversion to hypertensive levels.

The large variation in the amount of drug required by different subjects led us to look for possible correlations. Accordingly, the subjects were divided into "sensitive" and "resistant" groups, representing the upper and lower halves of the hexamethonium dosage range, respectively (table 1). The dividing line between the two groups lay at approximately 4 mg. of hexamethonium chloride per square meter of body surface area. The quantitative values of the various clinical characteristics were also averaged and the two groups were compared. Where differences in means were found, their significance was evaluated by the $t$ test.

The results of these calculations failed to demonstrate significant differences in pretest blood pressure, pulse rate, heart size, electrocardiographic patterns, funduscopic changes or known duration of hypertension. The only suggestive differences were the slightly greater

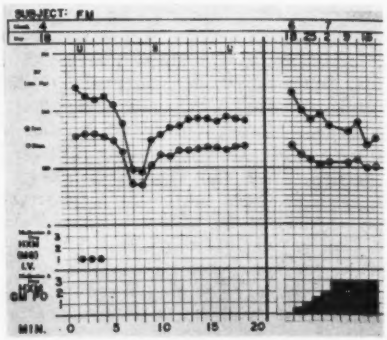


FIG. 4. A comparison of the intravenous hexamethonium test response (left) and the results of oral treatment (right) in patient F. M., a "sensitive" subject. *HXM MG IV* = intravenous hexamethonium dosage (milligrams per increment of drug). *HXM GM PO* = oral hexamethonium dosage (grams per day); *U* = patient upright; *S* = patient supine.

age ($t = 1.75$; $p < 0.10$) and higher blood nonprotein nitrogen concentration ($t = 2.17$; $p < 0.05$) of the sensitive group. Six of this group showed levels above 40 mg. per 100 cc., as compared with only one in the resistant group.

When the results of oral hexamethonium treatment were reviewed, it was found that the minimum pressure attained during therapy was highly correlated with the intravenous test dose ($r_{xy} = 0.576$; $t = 3.07$; $p < 0.01$);

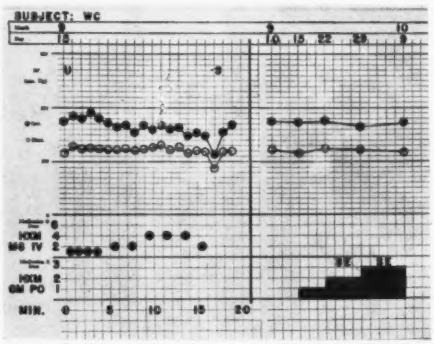


FIG. 5. A comparison of the intravenous hexamethonium test response (left) and the results of oral treatment in patient, W. C., a "resistant" subject. *HXM MG IV* = intravenous hexamethonium dosage (milligrams per increment of drug); *HXM GM PO* = oral hexamethonium dosage (grams per day); *U* = patient upright; *S* = patient supine; *SE* = presence of parasympatholytic side effects.

which is to say that the smaller the intravenous dose required, the greater was the maximum reduction in pressure under oral treatment. The subject group which was sensitive to intravenous hexamethonium responded to oral therapy by a blood pressure reduction to normal (fig. 3). In contrast, the resistant subjects as a group showed a maximum fall to 177 mm. Hg systolic, 105 mm. diastolic.

The sensitive group also differed from the resistant group in the frequency of postural hypotension during oral therapy, as evidenced by a marked drop in pressure between the sitting and standing positions, and by orthostatic dizziness and syncope. One or both signs occurred in 6 of 10 sensitive subjects, as compared with 2 of 11 resistant individuals. Parasympatholytic side effects were about equally prominent in the two groups, indicating that variations in absorption were not responsible for the lack of hypotensive activity in the resistant group.

A third difference between groups was the rapidity with which tolerance was developed for the hypotensive effect during oral therapy. The maximum reduction in pressure was reached early in the resistant group, after an average treatment period of two and one half weeks. In the sensitive group, on the other hand, the pressure continued to fall for about four and one half weeks, and the subsequent escape to hypertensive levels was slow.

Neither group developed much tolerance for parasympatholytic side effects. The drug usually had to be discontinued because of failure to maintain a pressure reduction commensurate with the difficulties of constipation, xerostomia, blurred vision or urinary retention.

The results in the two groups are typified by the favorable clinical course of a sensitive individual (fig. 4), and the failure of response in a resistant subject (fig. 5), who received the same daily doses of oral hexamethonium chloride.

## Discussion

The results of this study indicate that hypertensive patients can be classified as sensitive or resistant to the hypotensive action of hexamethonium chloride on the basis of the amount of intravenous drug required to produce a standard fall in pressure. No completely satisfactory explanation for this variation in sensitivity was found in the clinical status of these patients. One of the responsible factors appeared to be an impairment of renal excretory function. Under these circumstances a delay in metabolism and excretion of the drug may have made a smaller dose more effective and persistent as a ganglionic blocking agent.

None of the findings suggested that any major part of the hypertension in these subjects was due to vasoconstriction which was not under autonomic control. The blood pressure of both sensitive and resistant subjects was brought into the normal range with about equal frequency, when sufficient hexamethonium chloride was injected. The minimal rise in pulse rate during hexamethonium-induced hypotension indicated that cardioaccelerator, as well as vasoconstrictor fibers, were blocked effectively in the great majority of both sensitive and resistant subjects. The results do not exclude the possibility that autonomic control of vasoconstriction may be mediated through humoral factors. In support of this possibility is Grimson's finding[6] that experimental neurogenic hypertension persisted in otherwise completely sympathectomized dogs until the autonomic nerve supply to the kidneys was cut; whereupon blood pressure fell to normal limits.

The therapeutic responses in these subjects suggest that the intravenous hexamethonium test may have use as a guide to the maximum pressure reduction which can be anticipated from oral treatment, and to the rapidity with which tolerance may develop for the hypotensive action. The reported failure of others[7] to correlate intravenous sensitivity and oral effectiveness may have been due to differences in the criteria used to quantitate these actions. The rapid development of tolerance for the oral hypotensive effect makes the therapeutic evaluation particularly difficult.

## Summary and Conclusions

Twenty-three hypertensive subjects were tested with intravenous hexamethonium

chloride in an effort to determine the frequency and extent of blood pressure elevation not susceptible to reduction by ganglionic blockade. Twenty-one of the subjects were also studied to find out if the responses to oral hexamethonium therapy could be anticipated from the amount of intravenous drug required to produce a standard (50 per cent) fall in pressure.

The intravenous dose needed to produce this standard reduction varied from 1.4 to 23.0 mg. per square meter of body surface area. A comparison of the clinical characteristics of the "sensitive" and "resistant" halves of the group (as determined by a dosage requirement of less or more than 4 mg. per square meter, respectively) failed to show differences in pretest systolic or diastolic blood pressure, pulse rate, heart size, electrocardiographic patterns or known duration of the disease. "Sensitive" subjects were, in general, somewhat older and had suffered a greater deterioration in renal excretory function. Delay in renal metabolism or excretion of hexamethonium appeared to be one of the factors which may have been responsible for the differences in individual sensitivity.

No "irreversible" hypertensions were encountered. Nor was any evidence secured that a major part of the hypertension in any subject was due to vasoconstriction not under autonomic control. Reductions to normal were about equally frequent in sensitive and resistant subjects when sufficient hexamethonium was injected.

During oral hexamethonium treatment the "sensitive" group showed a reduction to normal pressure levels, a high incidence of postural hypotensive reactions and a delayed development of tolerance for the hypotensive effect. In contrast, the "resistant" group showed a much smaller maximum fall in pressure, a low incidence of postural hypotension and rapid development of tolerance for the hypotensive effect.

On the basis of these results, it is concluded that the intravenous hexamethonium test may be of some use in anticipating the responses of patients to oral hexamethonium treatment.


### Sumario Español

Este estudio representa un esfuerzo para distinguir entre los factores vasoconstrictores humorales y neurogénicos en un grupo representativo de pacientes hipertensos mediante la repuesta al bloqueo ganglionar del hexamethonium. La correlación entre la sensibilidad al hexamethonium intravenoso y la repuesta a tratamiento subsiguiente también se determinó.


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# The Treatment of Shock Associated with Myocardial Infarction

*By* GEORGE C. GRIFFITH, M.D., W. B. WALLACE, M.D., BURT COCHRAN, JR., M.D., W. E. NERLICH, M.D., AND W. G. FRASHER, M.D.

As a background to the problem of shock associated with acute myocardial infarction, a review of 816 recent consecutive and proved cases has been made. One hundred and sixty-one cases met the arbitrary criteria for the definition of shock. Therefore, shock was found to have occurred in 20 per cent of the patients with myocardial infarction. The mortality was 81 per cent (128 patients died). In the present study, 134 patients with acute myocardial infarction in shock were treated. All of these patients were first treated by strictly routine measures, including digitalis when indicated. Sixty of the 134 patients were relieved by prompt routine therapy given within a three-hour period of time. The remaining 74 patients were treated by (1) retrograde arterial infusion, (2) the newer sympathomimetic drugs such as methoxamine, isopropylnorepinephrine and norepinephrine and (3) other agents such as cholinesterase and cortisone. An evaluation of these methods was made and the over-all mortality of shock as associated with myocardial infarction was reduced from 81 per cent to 48 per cent.

CONSIDERABLE controversy exists concerning the value of various measures employed in the treatment of shock accompanying acute myocardial infarction. In spite of the high mortality rate attending this condition, antishock measures rarely have been instituted until considerable time has elapsed and hope for spontaneous recovery has been abandoned. In fact, hopelessness often has been the criterion for treatment. It is noteworthy, therefore, that results of an investigation recently completed at the Los Angeles County Hospital disclose that the *promptness with which measures for combating shock are instituted is a key factor in recovery*, overshadowing in importance the particular method or combination of methods used in bringing shock under control.

In this paper, evidence is presented of the importance of the time element in the successful treatment of the shock syndrome when associated with myocardial infarction. Also, results obtained with various modes of treatment at the Los Angeles County Hospital during an 18-month period in 1951 and 1952 are discussed. Statistics for a comparable 18-month period (1949–51) in which specific antishock measures were not employed afford an additional basis for evaluation of measures employed in the treatment of shock in the 1951–52 period.

### *Shock Defined*

For the purposes of this investigation, shock is defined as a condition of marked hypotension, lasting for an hour or longer, and accompanied by signs of peripheral circulatory collapse. In a patient whose blood pressure has previously been within normal limits, a systolic blood pressure reading of 80 mm. Hg or below is accepted as evidence of shock. In the formerly hypertensive patient, a systolic blood pressure of 100 mm. Hg or below evidences shock.

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We are indebted to the Los Angeles County Hospital Research Committee for assistance. We are privileged, too, to acknowledge the generous financial assistance of an anonymous donor.

The cholinesterase used in this study was supplied by Cutter Laboratories, the norepinephrine and isopropylnorepinephrine by Winthrop-Stearns, Inc., the methoxamine by Burroughs Wellcome & Co., and the Cortisone by Merck & Co., Inc.

## Material

*The Control Group.* A review of the records of the Los Angeles County General Hospital discloses that during an 18-month interval in 1949–1951, 816 patients gave proof of myocardial infarction, the diagnosis having been established by incontrovertible electrocardiographic evidence or verified at necropsy. One hundred and sixty-one of the 816 evidenced shock as defined in this investigation, a shock incidence of 19.7 per cent; of these 161 cases, 128 died, a mortality incidence of 80 per cent.

*The Experimental Group.* The experimental group was composed of 134 patients who were treated for shock coupled with unmistakable recent myocardial infarction during the 18-month period of this investigation (1951–1952). If the percentage of shock mortality approximated that of the control period, we could assume that 107 of the 134 patients would die. Our records show that only 64 patients died; a shock mortality incidence of 47.8 per cent.

## Methods of Treatment and Results

### *Importance of Time Element*

As stated earlier, the promptness with which measures for combating shock were instituted was of paramount importance: of the 134 patients with myocardial infarction treated for shock during the 1951–1952 interval, 60 received treatment within three hours of the onset of the shock syndrome. Of the 60, only 13 per cent died. In contrast of 74 patients who received treatment after lapse of a three-hour interval, 76 per cent died. (See table 1.)

Table 1.—*Results of Treatment Shock Associated with Myocardial Infarction*

| | No. of Cases | Survived, % |
|---|---|---|
| Control Group (1949–51) | 161 | 19 |
| Test Group (1951–52) | 134 | |
| (1) *Treated within 3 hrs.* | 60 | 87 |
| (2) *Treated after 3 hrs.* | 74 | 24 |

### *Routine Methods of Treatment*

All 134 patients were first treated by such obvious routine measures as proper positioning, relief from pain and cold, easing of anxiety, and control of other factors which might contribute to shock. Continuous administration of oxygen to each patient through a nasal catheter or mask, or by means of intermittent positive pressure, assured a sufficient supply of oxygen at all times. Phlebotomy or administration of ethyl alcohol vapor was required in instances of persistent failure.

Morphine sulfate, administered intravenously, proved of value in relieving shock, a pressor effect occurring promptly even in comatose patients. (We feel that morphine's advantages outweigh certain undesirable features, such as the aggravation of anoxemia by respiratory depression. Nevertheless, overtreatment with morphine can be detrimental, particularly in the elderly patient.)

Patients with congestive heart failure received intravenous doses of digitalis, strophanthus or other glycosides in order to support fully the uninfarcted myocardium. In the absence of heart block, premedication with quinidine proved a worthwhile procedure.

Arrhythmias were quickly brought under control, and anticoagulants were administered routinely unless a definite contraindication existed.

### *Additional Treatment*

If shock was not relieved by "routine" methods, additional measures were tried. Nine patients received *intravenous infusions:* a pressor effect was obtained in three instances, and shock was controlled in two.

*Retrograde arterial infusions* were given to 25 patients. A pressor effect was obtained in 19 cases; in 12 of these, shock was brought under control. A detailed analysis of results in 12 cases receiving arterial infusions will be found in table 2. Although a bulky apparatus was used in the first of the infusions, a simplified, portable apparatus similar to that described by Page has proved more suitable.[1] Any available artery can be used; it has, however, been our practice to insert large-

TABLE 2.—*Arterial Infusion in Coronary Shock. An Analysis of 12 Cases*

| Age | Sex | Shock Hours | Agent *cc.* | Adjunct Pre—Post | Infarct | Relief Hours | Fate | Comment |
|---|---|---|---|---|---|---|---|---|
| 69 | F | 24 | B-500 | ivP, B—V | Anteroseptal | 3 | Died 5½ hrs. | 3° heart block |
| 72 | F | 4½ | B-300 | iv, V—ivB, V | Anteroseptal | 13 | Died 31 hrs. | Embolism<br>Perforated peptic ulcer |
| 70 | F | 6 | B-500<br>Lac-90 | Routine | Posteroseptal | 63 | Died 65 hrs. | 3° heart block<br>Arrhythmia<br>Pneumonia |
| 77 | M | 6 | B-500<br>d/s-900 | ivP—<br>ivP— | Posteroseptal | * | Died 34 hrs. | Arrhythmia |
| 65 | M | 6 | P-250 | V—V | Anterior | * | *Lived | |
| 63 | M | 4 | B-500 | Routine | Anterior | * | *Lived | |
| 71 | F | 3 | d/s-1000, B-500 | V—V | Antero-posterior | * | Died 13 days | Cardiac tamponade |
| 58 | M | 20 | P-500 | R—RAI | Anterior | 3 | Died 4 hrs. | Repeat RAI to no avail |
| 67 | M | 7 | P-250 | V—V, C | Anterior | 3 | Died 4 hrs. | Cortisone |
| 78 | M | 5 | P-250 | V—V | Anterior | * | *Lived | Embolism |
| 38 | M | 6 | P-250 | V—G, V | Anterior | * | *Lived | Cortisone |
| 55 | M | 3 | B-275 | V—R | Anterior | * | *Lived | |

*Shock Hours:* Hours in shock before arterial infusion.

*Adjunct Pre—Post:* Treatment before and after arterial infusion B (*whole blood*), P (*plasma*), Lac (*M/6 sodium lactate*), d/s (*5% glucose in normal saline*), iv (*intravenous*), V (*vasopressor drugs*), R (*routine coronary regimen*), RAI (*retrograde arterial infusion*), C (*Cortisone*).

*Relief Hours:* Time in hours shock was relieved. * Permanent relief of shock.

*Fate:* Figures indicate time after completion of arterial infusion that the patient expired.

gauge polyethylene tubing into the radial artery just proximal to the styloid process. In considering our results (table 2), it should be noted that we have employed lower perfusion pressures than are commonly reported, and that the infusion times have been prolonged accordingly. (Perfusion pressures were generally 100 to 140 mm. Hg, but lower in a few instances; the duration of infusions was usually 20 to 70 minutes, but in a few instances longer.) Plasma or blood has been employed in most instances.

One hundred and five episodes of shock were treated with three of the newer sympathomimetic amines: norepinephrine, methoxamine, and isopropylnorepinephrine. Each has proved of value, particularly with early treatment.

*Norepinephrine.* Early reports on the effects of norepinephrine suggested that an apparent tendency of the preparation to produce ventricular arrythmias might constitute a considerable hazard in the presence of myocardial infarction.[2] Later reports have been more encouraging. Norepinephrine has been employed without untoward effects in the treat-

ment of hypotension following thoracolumbar sympathectomy,[3] and, more recently, has received clinical trial in the treatment of seven patients with coronary shock.[4] Ventricular irritability did not follow. Norepinephrine was used in 30 cases; shock was controlled in 17 of these. We have been impressed with the effectiveness of norepinephrine when used early in shock, or when employed late in the treatment after other pressor amines have failed.

Administration was as follows: 1000 cc. of 5 per cent glucose in water to which two vials (8 mg.) of norepinephrine had been added were supplied by intravenous drip through a polyethylene tube introduced for a distance of six or eight inches into the antecubital vein. Drip was begun at an initial rate of 10 drops per minute—delivering 8 gamma per minute—and rate of drip was increased or slowed as necessary to maintain a systolic blood pressure of 120. Drip was continued for as long as required (even as long as 72 hours). It is important that blood pressure be taken every 15 or 20 minutes.

*Methoxamine.* Forty-nine patients received methoxamine. Pressor effect was obtained in 14 patients and shock controlled in 10 patients. No pressor effect was obtained in 35 instances: this we attribute in part to the fact that response to the drug is lost relatively early in shock. Methoxamine proved useful within the first few hours of shock, usually as an adjunct to other therapy.

Methoxamine was administered either intramuscularly (20 mg. dose) or intravenously (5 mg. dose, given slowly and repeated as needed).

*Isopropylnorepinephrine.* Twenty-six patients were given isopropylnorepinephrine. A pressor response was obtained in 10 patients, while shock was controlled in seven patients. No pressor effect was seen in 16 patients. This drug has proved particularly useful in cases of shock associated with complete heart block, bundle branch block or prolonged congestive failure. Although isopropylnorepinephrine's action in coronary shock has not been established with definiteness, its inotropic and chronotropic cardiac effects are presumably accompanied by medullary stimulation, coronary dilation, and relief from excessive peripheral vasoconstriction.

Two or 3 mg. of isopropylnorepinephrine are given slowly intravenously, followed by 7.5 or 15 mg. given under the tongue as needed after shock has been overcome (at 10 to 15, or at 30 minute intervals).

*Comparison of the Effects of Epinephrine, Norepinephrine, Isopropylnorepinephrine and Methoxamine.* A comparison of the effects of these four drugs as observed by us is worthy of note. (See table 3.) In the patients in shock with an intact conduction system, epinephrine, norepinephrine and methoxamine raise the blood pressure, while isopropylnorepinephrine fails to do so. The heart rate is increased by epinephrine and isopropylnorepinephrine. Norepinephrine has no effect on the rate. Methoxamine slows the heart rate. Epinephrine and norepinephrine stimulate an already sensitized myocardium in the experimental animal. In our experience there has been no unusual arrhythmia noted from the use of norepinephrine in small or large doses when regulated by the pressor response. In patients in shock where there is complete auriculoventricular disassociation isopropylnorepinephrine not only increases the ventricular rate preventing Adams-Stokes attacks but also has demonstrated a remarkable pressor effect.

TABLE 3.—*A Comparison of Hemodynamic Effects of Some Sympathomimetic Amines*

| Effect On: | Epinephrine | Norepinephrine | Isopropylnorepinephrine | Methoxamine |
|---|---|---|---|---|
| Systemic blood pressure | + | + | *− | + |
| Normal sinus rhythm (rate) | + | − | + | − |
| 3° heart block (ventricular rate) | + | 0 | + | 0 |
| Total peripheral resistance | − | + | − | + |
| Cardiac output | + | 0 | + | 0 |
| Stimulation of sensitized myocardium | + | + | ± | 0 |

* Normotensive adult volunteers; in shock blood pressure is raised (see text).

\+ (*increase*), 0 (*no change*), − (*decrease*)

*Dosages.* Dosage schedule of these sympathomimetic amines must be adjusted so as to maintain a sustained beneficial arterial pressure. In most instances, the continuous intravenous drip method of administration is most satisfactory. Combinations of the amines often prove effective when the individual drug has failed to produce the desired result. Although response to customary doses may be absent during prolonged periods of shock, a judicious increment in dosage may be beneficial.

*Methods of Restoring Vasopressor Response*

In spite of treatment, patients with myocardial infarction frequently lapse into a refractory state of chronic shock, in which they may remain for a surprising number of hours before death. This observation has prompted a search for a means of restoring lost response to antishock therapy. C-11 oxysteroids (cortisone) and cholinesterase have been used for this purpose in our investigation, in combination with other measures used to combat shock. Our findings are not in agreement with those in a recent report by Kurland and Freedburg,[6] who noted potentiation of the blood pressure response to norepinephrine within 24 hours of the administration to normotensive subjects of 90 to 180 mg. of adrenocorticotropic hormone (ACTH) daily, or 150 to 200 mg. cortisone daily. In 12 cases of myocardial shock cortisone was administered as an adjunct medicament with no pressor response in 11 patients and very questionable control of shock in one patient.

Cholinesterase was administered in increasing dosage hoping for a pressor effect in 10 patients with myocardial shock. In one case there was a doubtful response while in the other 9 cases there was no response seen.

Table 4 gives a comparison of all measures used to combat shock during the period of investigation, including the administration of cortisone and cholinesterase.

TABLE 4.—*Measures Employed to Combat Shock*

| Treatment | No. of Cases | Pressor Effect | | No Pressor Effect |
|---|---|---|---|---|
| | | Shock Controlled | Shock Uncontrolled | |
| Venous infusion | 9 | 2 | 1 | 6 |
| Retrograde Arterial infusion | 25 | 12 | 7 | 6 |
| Newer Sympathomimetic Amines | | | | |
| (1) Norepinephrine (Levophed) | 30 | 17 | 2 | 11 |
| (2) Methoxyamine (Vasoxyl) (Wyamine) | 49 | 10 | 4 | 35 |
| (3) Isopropylnorepinephrine (Isuprel) | 26 | 7 | 3 | 16 |
| Cortisone | 12 | 1 (?) | 0 | 11 |
| Cholinesterase | 10 | 1 | 0 | 9 |

## Conclusion

The promptness with which anti-shock treatment is instituted is apparently more important than the particular method used. "Routine" measures, venous infusions, retrograde arterial infusions, and the newer sympathomimetic amines are all of value in the treatment of shock associated with myocardial infarction. Cortisone and cholinesterase may be of value in restoring lost responses to antishock therapy.

## Sumario Español

Como un fondo al problema del choque asociado al infarto del miocardio agudo, se han revisado 816 casos recientes consecutivos y comprobados. Ciento sesenta y un casos llenaron el criterio arbitrario para la definición de choque. Demanera que hubo una incidencia de 20 por ciento de choque en los pacientes con infartos del miocardio. La mortalidad fué de 81 por ciento (128 pacientes murieron). En el presente estudio, 134 pacientes con infartos agudos del miocardio en choque fueron tratados. Todos estos pacientes fueron tratados primeramente con medidas puramente rutinarias, incluyendo digital cuando estuvo indicado. Sesenta de los 134 pacientes fueron mejorados con la terapia rutinaria pronto administrada en un período de tiempo de tres horas. Los restantes 74 pacientes fueron tratados con (1) infusión retrograda arterial (2) las nuevas drogas simpatomiméticas como me-

thoxamine, isopropylnorepinephrine y norepinephrine y (3) otros agentes como colinesterasa y cortisona. Una evaluación de estos métodos se hizo y la mortalidad general del choque asociada al infarto del miocardio se redujo de 81 por ciento a un 48 por ciento.

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# The Incidence and Severity of Atherosclerosis in Estrogen-Treated Males, and in Females with a Hypoestrogenic or a Hyperestrogenic State

*By* ARTHUR U. RIVIN, M.D. AND SIM P. DIMITROFF, M.D.

Autopsy records of estrogen-treated men, castrated women, and women with breast carcinoma were analyzed with reference to the degree of atherosclerotic disease. Findings were then compared with those in similar groups of men and women whose estrogen supply was considered normal. Results obtained suggest: (1) that the male treated with estrogen has less atherosclerosis than the normal male; (2) that the oophorectomized female has an incidence of severe atherosclerosis approaching that of the male; and (3) that the hyperestrogenic female with breast carcinoma has less atherosclerosis than the normal female.

THE REMARKABLE sex difference in the incidence of atherosclerosis[4, 12, 17] suggests that estrogenic hormones may exert an inhibitory effect on the pathogenesis of this disease. In order to explore this possibility, clinical and autopsy statistics were compiled in groups of patients who demonstrated deviations from their normal estrogen supply. Hyperestrogenism in males was studied in patients with carcinoma of the prostate who were treated with estrogens. Hyperestrogenism in females was considered to be present in women with carcinoma of the breast.[10, 23] The hypoestrogenic state was studied in a group of surgically castrated females. The incidence and severity of atherosclerosis in these patients were then compared with that in similar groups who were apparently normal with reference to their estrogen supply.

## MATERIALS AND METHODS

Autopsy protocols and clinical histories of 153 patients with carcinoma of the prostate were examined. Of these patients 53 were given estrogen therapy for three months or more, 100 received estrogen for less than three months or no hormone at all. The severity of atherosclerosis was compared in the two groups. The selection of three months as the dividing line between the two groups was more or less arbitrary, but was used because it was the minimum length of treatment time at which gynecomastia was noted to appear. Thus it was considered the minimum effective duration of estrogen therapy. The ages of the patients ranged from 46 to 91, with an average age of 69. There was no significant age difference between the treated and untreated groups. The maximum duration of hormonal treatment was seven years, and the average duration 16 months. The average daily dosage of stilbesterol was 75 mg. or more in one group of patients (Wadsworth Hospital). It was 5 mg. or less in another (Los Angeles County Hospital). The two series were tabulated separately, so that any divergence in findings might be observed.

The second portion of the study was devoted to determining the changes in the atherosclerotic process induced by oophorectomy and the hypoestrogenic state. Autopsy and clinical records of oophorectomized women at Los Angeles County Hospital were analyzed. All were patients who had had bilateral oophorectomy before the age of 50, and at least one year before the time of death. Such requirements were stipulated in order to eliminate, in so far as possible, the effect of naturally occurring ovarian atrophy. The maximum interval between oophorectomy and death was 35 years, the minimum one year, and the average five years.

The third phase of this paper represents a study of atherosclerosis in the hyperestrogenic state. The series of cases of breast carcinoma, containing 39 patients, was also studied at the Los Angeles County Hospital.

In these studies note was made of the state of

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nutrition at the time of death, the age, associated diseases, areas of metastasis of tumor when present, dosage and duration of administration of estrogen and other methods of treatment, including oophorectomy or orchiectomy. In males, evidences of feminization, particularly gynecomastia, were recorded.

The degree of atherosclerosis in three sites, the coronary arteries, aorta, and brain was tabulated. While the autopsy surgeons used the terms none, minimal, moderate, moderately severe, and severe, to describe the degree of arterial narrowing, only two classification categories were used in this study: minimal or none, and moderate or severe.

Diabetics, nephrotics, and patients with other causes for hypercholesterolemia, were eliminated from the series. Hypertensive subjects, however, were included, since it was impossible in arranging the chronology of hypertension and atherosclerosis to decide which of the abnormalities had developed first.

Because it is the commonly held concept that undernutrition reduces the amount of atherosclerosis[1, 27] all comparisons were first made between the well nourished and the poorly nourished groups. It was found that of the cachectic group, 63 per cent had severe atheromatosis, whereas of the well nourished, 69 per cent were so afflicted. For this reason it was decided to include all cases, regardless of nutrition, in all three sections of the study.

## Results

The statistical significance of the data presented is estimated by considering the 95 per cent fiducial limits of the observed sample proportions. If the fiducial limit percentages listed in comparing one group with another do not overlap, then it can be concluded that the possibility of chance sampling having produced the apparent difference is less than 1 in 20. On the other hand, if there is overlap in the comparative fiducial limit percentages then the difference is not considered to be statistically significant.[5]

Table 1 summarizes the prostatic carcinoma series in which larger doses of estrogens, 75 mg. of stilbesterol or more, were given daily. It demonstrates that there is less atherosclerosis in the estrogen-treated group. Thus of a total of 30 estrogen-treated cases, 11 had severe coronary atherosclerosis. On a simple percentage basis one could then conclude that 36.6 per cent had severe coronary artery disease. However, using the method of fiducial-limit analysis to determine what the percentage range might be if a much larger series of cases was studied, we find that the figure might range from 22.1 to 53.3 per cent. This computation is made in order to eliminate the possibility that chance alone, and not factual observation, may produce a finding more indicative of luck than of reality.

Similarly, the fiducial limit percentage range for severe coronary artery disease in the untreated group is 73.3 to 90.0. When we compare the boundary figures for the two groups we note that they do not cross and that the percentage ranges are mutually exclusive. Consequently the conclusions are that pure chance cannot be responsible for the differences observed and that the administration of estrogen to one group probably reduced its incidence of severe atherosclerosis in the coronary arteries.

Attention is called to the comparative fiducial limit ranges in the aorta and cerebral artery sites. Here the figures do show overlap and one must conclude that they are not of statistical significance.

While most of these patients were treated with stilbesterol, seven had 0.1 mg. per day of Estinyl or 1.25 mg. per day of Premarin alone or in combination with stilbesterol. All of these latter at postmortem examination showed

Table 1.—*Comparison of Atherosclerosis in Patients with Carcinoma of the Prostate Treated with Large Doses of Estrogens and Those Receiving no Estrogen or Estrogen for Less Than Three Months*

(*Wadsworth Hospital*)

| Site | Severity of Atherosclerosis | Incidence in pts. treated with estrogen 3 mos. or more | | Incidence in pts. treated with no estrogen or estrogen for less than 3 mos. | |
|---|---|---|---|---|---|
| | | No. pts. | Fiducial limits % | No. pts. | Fiducial limits % |
| Coronary Arteries | Minimal or none | 19 | | 3 | |
| | Moderate or severe | 11 | 22.1–53.3 | 24 | 73.7–90.0 |
| Aorta | Minimal or none | 7 | | 1 | |
| | Moderate or severe | 23 | 61–89 | 26 | 84–99 |
| Cerebral Arteries | Minimal or none | 10 | | 1 | |
| | Moderate or severe | 10 | 31–70 | 9 | 61–99.5 |

TABLE 2.—*Comparison of Atherosclerosis in Patients with Carcinoma of the Prostate Treated with Small Doses of Estrogen and those Receiving no Estrogen or Estrogen Less than Three Months*

(*Los Angeles County Hospital*)

| Site | Severity of Atherosclerosis | Incidence in pts. treated with estrogen 3 mos. or more | | Incidence in pts. treated with no estrogen or estrogen for less than 3 mos. | |
|---|---|---|---|---|---|
| | | No. pts. | Fiducial limits % | No. pts. | Fiducial limits % |
| Coronary Arteries | Minimal or none | 10 | | 22 | |
| | Moderate or severe | 13 | 38–74 | 51 | 58–80 |
| Aorta | Minimal or none | 5 | | 18 | |
| | Moderate or severe | 18 | 60–91 | 58 | 63–85 |
| Cerebral Arteries | Minimal or none | 4 | | 8 | |
| | Moderate or severe | 4 | 19–81 | 21 | 56–86 |

minimal atherosclerosis of all sites studied. In the group of 19 men showing minimal or no coronary atherosclerosis, 15 had enough estrogen to produce gynecomastia. All who had gynecomastia due to administered estrogen had minimal coronary atherosclerosis.

Table 2 shows the findings in another series of prostatic carcinoma patients studied at the Los Angeles County Hospital. In this group an average dosage of 5 mg. per day was employed which is much lower than that used in the Wadsworth series. Twenty-three patients were treated with estrogens and 73 were not. Note that all of the estrogen-treated fiducial limit figures range into the fiducial percentages of the untreated column. Therefore none of the comparative data in this table is considered significant.

Convincing evidence of estrogenic protection against atherosclerosis is lacking in the patients studied at the County Hospital. It may be that the 5 mg. daily dosage of stilbesterol was insufficient to produce an antiatherogenic effect. If estrogens are protective, their action may be a function of the dosage administered.

The effect of bilateral oophorectomy performed one year or more prior to death is shown in table 3. These data reveal a remarkably high incidence of atherosclerosis, even below age 60, in women who had been castrated.

Table 4 presents data concerning the incidence of atherosclerosis in the hyperestrogenic state in females as represented by breast carcinoma patients. Atherosclerosis in this group appears to be rare when compared with the incidence in the normoestrogenic female. Figure 1 will illustrate this difference. Table 5 offers a statistical analysis of the differences between the oophorectomized, and the hyperestrogenic group. All the data point in one direction: toward a higher incidence of atherosclerosis in the oophorectomized female. In the case of the coronary arteries in the age groups above 60, the figures establish beyond the realm of chance a real difference between the hypoestrogenic and the hyperestrogenic females.

Figure 1 graphically summarizes the incidence of severe coronary atherosclerosis in the two female groups noted above and compares this form of atherosclerosis in the abnormal endocrine states studied with the incidence of coronary artery disease in 600 women, ages 30 through 89, reported by Ackerman, Dry,

TABLE 3.—*Incidence and Severity of Atherosclerosis in Castrated Females*

| Age Group | Site | Incidence of atherosclerosis graded minimal or none | | Incidence of atherosclerosis moderate or severe degree | |
|---|---|---|---|---|---|
| | | No. pts. | % | No. pts. | % |
| 35–50 | Coronary arteries | 18 | 75 | 6* | 25 |
| | Aorta | 14 | 58 | 10 | 42 |
| | Cerebral arteries | 7 | 58 | 5 | 42 |
| 51–60 | Coronary arteries | 7 | 50 | 7 | 50 |
| | Aorta | 5 | 42 | 7 | 58 |
| | Cerebral arteries | 8 | 88 | 1 | 12 |
| 61–70 | Coronary arteries | 12 | 32 | 25 | 68 |
| | Aorta | 9 | 24 | 28 | 76 |
| | Cerebral arteries | 9 | 42 | 10 | 58 |
| 71–100 | Coronary arteries | 4 | 25 | 12 | 75 |
| | Aorta | 2 | 13 | 14 | 87 |
| | Cerebral arteries | 2 | 25 | 6 | 75 |

* Of the hypertensives in the age group 35–50, five had severe and one no coronary disease. There were no hypertensives age 51–60. Of the group 61–70, four hypertensives showed severe, and two minimal coronary disease. Of the oldest group, there were three hypertensives, one with minimal and two with severe atherosclerosis.

TABLE 4.—*The Incidence and Severity of Atherosclerosis in Patients with Carcinoma of the Breast*

| Age Group | Site | Incidence of atherosclerosis graded minimal or none | | Incidence of atherosclerosis moderate or severe degree | |
|---|---|---|---|---|---|
| | | No. pts. | % | No. pts. | % |
| 41–50 | Coronary arteries | 7 | 100 | 0 | 0 |
| | Aorta | 7 | 100 | 0 | 0 |
| | Cerebral arteries | 7 | 100 | 0 | 0 |
| 51–60 | Coronary arteries | 10 | 83 | 2 | 17 |
| | Aorta | 8 | 80 | 2 | 20 |
| | Cerebral arteries | 10 | 100 | 0 | 0 |
| 61–70 | Coronary arteries | 15 | 88 | 2 | 12 |
| | Aorta | 11 | 65 | 6 | 35 |
| | Cerebral arteries | 12 | 86 | 2 | 14 |
| 71–100 | Coronary arteries | 6 | 83 | 1 | 15 |
| | Aorta | 3 | 50 | 3 | 50 |
| | Cerebral arteries | 5 | 83 | 1 | 17 |

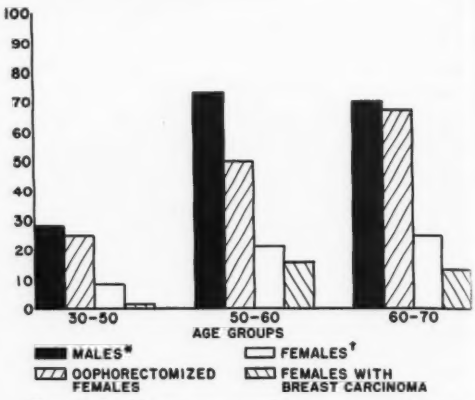


FIG. 1. Incidence expressed in per cent of severe coronary atherosclerosis in oophorectomized hypoestrogenic females, in hyperestrogenic females with breast carcinoma and in normoestrogenic males and females.

* From White and co-workers.[29] † From Ackerman and co-workers.[1]

and Edwards.[1] Comparisons are also made with a group of 500 males of varying age groups reported by White.[26] Patients in both latter groups were studied consecutively as they came to autopsy, without regard to the cause of death. The criteria for grading the severity of atherosclerosis in these series compared with standards used in the present study were substantially the same.

Figure 1 shows that in the age group 30 to 50, the incidence of severe coronary sclerosis in castrated females almost equals that of males, whereas in females with breat carcinoma, it is minimal. In the age group 50 to 60 years, which is predominant for coronary sclerosis in males, the oophorectomized female has a high percentage of severe disease, while the female with breast carcinoma shows the least sclerosis. In age groups 60 to 70, the oophorectomized female again is almost equal to the male in the incidence of severe coronary artery disease.

TABLE 5.—*Comparison of Incidence of Severe Atherosclerosis in Hypoestrogenic Oophorectomized Females and Hyperestrogenic Females with Carcinoma of the Breast*

| Age Group | Site | Oophorectomized | | | Breast Carcinoma | | |
|---|---|---|---|---|---|---|---|
| | | No. cases with severe involvement | Total no. cases studied | Fiducial limits % | No. cases with severe involvement | Total no. cases studied | Fiducial limits % |
| 35–50 | Coronary arteries | 6 | 24 | 11–44 | 0 | 7 | 0–35 |
| | Aorta | 10 | 24 | 25–60 | 0 | 7 | 0–35 |
| | Cerebral arteries | 5 | 12 | 18–69 | 0 | 7 | 0–35 |
| 51–60 | Coronary arteries | 7 | 14 | 26–74 | 2 | 12 | 3–49 |
| | Aorta | 7 | 12 | 32–82 | 2 | 10 | 4–51 |
| | Cerebral arteries | 1 | 9 | 0.6–43 | 0 | 10 | 0–26 |
| 61–70 | Coronary arteries | 25 | 37 | 50–82* | 2 | 17 | 2–32 |
| | Aorta | 28 | 37 | 58–85* | 6 | 17 | 16–58 |
| | Cerebral arteries | 10 | 19 | 32–78 | 2 | 14 | 26–38 |
| 71–100 | Coronary arteries | 12 | 16 | 52–91* | 1 | 7 | 0.7–51 |
| | Aorta | 14 | 16 | 66–98 | 3 | 6 | 15–85 |
| | Cerebral arteries | 6 | 8 | 40–95 | 1 | 6 | 0.8–58 |

* No overlap in range of comparative fiducial limit percentages. Statistically significant.

## Discussion

Four groups of patients have been studied with reference to the incidence and severity of atherosclerosis. It was noted that among a group of males treated with high doses of estrogens, there was less intense atherosclerotic disease than in a comparable series of untreated males. An additional finding was the absence of significant coronary artery atherosclerosis in 15 of 19 patients who exhibited gynecomastia as a result of estrogen administration. A group of males who received small estrogen doses demonstrated no change from the untreated group.

In the group of female castrates there appeared to be an increased incidence of advanced atherosclerosis, particularly in the coronary arteries, as compared with the incidence in a normal female population. Similar findings were recently reported in a study from the Mayo Clinic.[28] Among the women with breast carcinoma, representing the hyperestrogenic state, atherosclerosis was minimal.

What are the implications of these findings? Many theories have been proposed to explain the sex dissimilarities in atherosclerosis.[13, 15] There is substantial experimental evidence to support the concept that the female hormones themselves may be the key factor.

In order for estrogens to reduce atheromata in the age group of the prostatic carcinoma patients, one would have to postulate not only protection from, but also actual reversal of well established disease. That this can occur in chickens has been demonstrated by the recent work of Pick and co-workers which showed estrogen-induced reversal of arterial disease to normal even after the development of fibrotic changes in the atheromata.[20] The same investigators have noted estrogen protection of the coronary arteries from atherosclerosis, without protection of the aorta.[19] These findings parallel the results of this study, indicating selective protection of the coronary arteries. In rabbits also, it is possible to prevent cholesterol-induced atherosclerosis by estradiol administration.[7] However (and this is the crucial point), the sex steroids' prophylactic effect was evident only in the female rabbit, and could not be demonstrated after castration.

Since abnormal plasma lipid relationships are implicated in the development of atherosclerosis,[3, 9, 18] the evidence for estrogen influence on the lipid partition is relevant to this discussion. Russ and associates have discovered that the normal female, age 18 to 35, has distinctly more alpha lipoprotein (with a low cholesterol–phospholipid ratio) than males of the same age group.[22] After age 45, no sex differences in lipid content were noted. The Gofman group, utilizing ultracentrifuge analysis, found that it is not until age 50 to 60 that the female reaches the concentration of the $S_f$ molecules most closely correlated with atherosclerosis, that the male had reached at age 30.[14] Such studies suggest that some factor operating at the peak period of sex-hormone activity accounts for the sex differences in lipid fractions. Eilert has noted that the administration of estrogens to menopausal women has altered their serum lipid levels, with a sharp reduction in the cholesterol–phospholipid ratio.[8] Glass and his co-workers have been unable to detect any effect of administered estrogens on lipoproteins.[11]

The biologic mechanisms by which estrogens affect the plasma lipids, and thereby, perhaps, atherosclerosis also, are certainly most obscure. The influences of the steroid hormones on each other,[24, 25] as well as on lipid metabolism[2, 6, 16, 21] indicate that the estrogen-lipid-atherosclerosis relationship must be a very complex one.

## Summary and Conclusions

1. Autopsy records have been utilized to draw a statistical comparison between the incidence and severity of atherosclerosis in patients who had deviations from their ordinary estrogen supply, and patients whose estrogen status was normal.

2. Four groups of cases have been studied: 57 patients with prostatic carcinoma, 30 of whom were given an average daily dose of 75 mg. of stilbesterol; 96 patients with prostatic carcinoma, 23 of whom were given an average daily dose of 5 mg. of stilbesterol; 99 female patients who had undergone castration; and

39 women who had carcinoma of the breast with probable accompanying hyperestrogenism.

3. These studies have demonstrated: (a) an apparent diminution of coronary atherosclerosis in males treated with large doses of estrogen; (b) a significant increase in atherosclerosis, especially in the coronary arteries, in women who have had their estrogen supply reduced by castration; (c) an incidence of severe atherosclerosis in the hyperestrogenic female even less than that of the normal female.

4. These findings lend support to the experimental evidence derived from animal studies which suggest that the female has less atherosclerosis than the male because ovarian secretions in some way protect from this disease.

5. Theoretic mechanisms involved in the action of sex hormones on lipid metabolism have been suggested.

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SUMARIO ESPAÑOL

1. Los protocolos de autopsia de pacientes con desviaciones de abastecimiento normal de estrógeno y pacientes con abastecimiento normal, han sido utilizados para obtener una comparación estadística entre la incidencia y la severidad de la ateroesclerosis en estos pacientes.

2. Cuatro grupos de pacientes han sido estudiados: 57 pacientes con carcinoma de la prostata, 30 de los cuales se les administró una dosis promedio de 75 mg. de estilbestrol; 96 pacientes con carcinoma de la prostata, 23 de los cuales se les administró una dosis diaria de 5 mg. de estilbestrol; 99 pacientes hembras que sufrieron castración; y 39 mujeres con carcinoma de la mama con probable hiperestrogenismo.

3. Estos estudios han demostrado: (a) una aparente diminución de ateroesclerosis coronaria en los varones tratados con dosis grandes de estrógeno; (b) un incremento significativo en ateroesclerosis, especialmente en las arterias coronarias, en mujeres que han tenido un abastecimiento de estrógeno reducido por castración; (c) la incidencia de ateroesclerosis severa en la hembra con carcinoma de la mama y hiperestrogenismo fué menor que la de la hembra normal.

4. Estos hallazgos prestan sostén a la evidencia experimental derivada de animales que sugiere que la hembra tiene menos ateroesclerosis que el varón debido a que las secreciones ováricas de alguna manera protegen de esta enfermedad.

5. Mecanismos teóricos envueltos en la acción de las hormonas sexuales en el metabolismo lípido han sido sugeridos.

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# A Clinical Appraisal of Pentapyrrolidinium (M&B 2050) in Hypertensive Patients

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The new ganglionic blocking agent, pentapyrrolidinium or M&B 2050, appears to have several distinct advantages over hexamethonium in the treatment of severe hypertension. These advantages include longer duration of action, greater potency, less tolerance, less interference with intestinal motility, and, most important, a more uniform response from day to day on oral administration. However, critical adjustment of dosage is necessary and side effects are not infrequent, the most disturbing being postural faintness and impotence.

THE advantages as well as the deficiencies of hexamethonium in the treatment of hypertensive patients[1, 2] have stimulated interest in the development of ganglionic blocking agents which will retain the desirable effects of hexamethonium and eliminate its undesirable qualities. By the very nature of its action it can be expected that any drug which acts by inhibiting transmission through autonomic ganglia will exhibit many of the side effects of such blockade. However, it seems possible that there may be differences in the predilection of various compounds for certain ganglia as compared with others; and also that other advantages might be gained, such as longer duration of action, lessened tolerance, greater and more predictable absorption from the gastrointestinal tract, which would decrease the hazards and inconveniences attendant upon hexamethonium administration.

Recently, a new ganglionic blocking agent, pentamethylene 1:5-bis-(1-methyl-pyrrolidinium bitartrate) (pentapyrrolidinium or M&B 2050) has been synthesized by Libman, Pain and Slack.[3]

Detailed pharmacologic studies in animals have been carried out by Wein and Mason.[4] Preliminary clinical trials by Campbell and Maxwell suggested that the new drug was more potent, longer-acting, and produced a more predictable response on oral administration than hexamethonium.[5] Smirk found that pentapyrrolidinium administered orally was more effective and better tolerated by hypertensive patients than was hexamethonium.[6] The purpose of the present report is to describe the experiences in this clinic with this new agent in hypertensive patients. For the sake of clarity all dosage of both hexamethonium and M&B 2050 will be referred to in terms of the amount of ion. Hexamethonium was administered in the form of the chloride and M&B 2050 as the bitartrate salt.

## Potency and Duration of Action of M&B 2050 as Compared with Hexamethonium

Four hospitalized hypertensive patients were given hexamethonium intravenously in an amount sufficient to produce a significant reduction of arterial pressure. Several days later pentapyrrolidinium was injected slowly intravenously until the fall of blood pressure was similar to that produced by the hexameth-

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TABLE 1.—*Comparison of Single Intravenous Dosages of Hexamethonium (C6) and Pentapyrrolidinium (M&B 2050) in Previously Untreated Hypertensive Patients*

| Patient | Blood Pressure | Reduction of Blood Pressure mm. Hg | | Change in Heart Rate Beats Min. | | Dose, mg. of Ion | | Duration of Effect In Hours | |
|---|---|---|---|---|---|---|---|---|---|
| | *mm Hg* | After C6 | After M&B 2050 | After C6 | After M&B 2050 | C6 | M&B 2050 | C6 | M&B 2050 |
| C. B. | 195/120 | 28/22 | 48/35 | 0 | −4 | 18 | 4 | 6 | 10 |
| R. C. | 220/145 | 65/30 | 72/38 | +16 | +18 | 50 | 7 | 6 | 10 |
| A. S. | 215/115 | 68/27 | 92/28 | −4 | −4 | 20 | 4 | 6 | 11 |
| P. D. | 185/135 | 60/20 | 50/30 | +18 | +16 | 12 | 3 | 5 | 9 |

onium. These patients had received no prior therapy with either agent.

On the basis of these acute comparative studies M&B 2050 was approximately five (range four to seven) times more potent than hexamethonium (table 1). The average duration of action of M&B 2050 also was 42 per cent (range 40 to 46 per cent) longer than that of hexamethonium.

During an intravenous titration with hexamethonium the blood pressure falls rapidly when the effective dose has been reached. When M&B 2050 is administered intravenously, however, the reduction in the blood pressure proceeds more gradually over a period of 10 minutes or more following an effective dose. Thus, intravenous titration with M&B 2050 is more difficult than with hexamethonium since the effective dose may be exceeded. This could be avoided in some measure by injecting the drug quite slowly with the patient sitting on the side of the bed, since postural hypotension appears before supine hypotension.

### Relation between Effective Parenteral and Oral Dosages of M&B 2050

Following intravenous titration 10 hypertensive patients were treated with M&B 2050 subcutaneously twice daily either in the hospital or, occasionally, in the home. If treatment was on an ambulatory basis, the blood pressure was recorded five times daily in the home. At the end of one week parenteral therapy was discontinued and the drug administered orally every eight hours. The dosages were increased every other day until the average daily blood pressure approximated that achieved during parenteral therapy.

The mean effective parenteral dose of M&B 2050 was 15 mg. per day, whereas the mean daily oral dose was 280 mg. Thus, the effective oral dose was approximately 20 times as great as the effective parenteral dose. This relationship between oral and parenteral dosage is similar to that previously observed with hexamethonium.[7] It also agrees in general with urinary recoveries of M&B 2050 in animals, which indicated that less than 20 per cent of an orally administered dose is absorbed.[8]

Pentapyrrolidinium given orally differed from hexamethonium administered orally in one important respect. The onset of action was far more predictable than with hexamethonium, beginning approximately one hour after an effective dose. There also was less variation from day to day in the response to a given dose of M&B 2050 than had previously been experienced with the response to hexamethonium.[2] However, as will be discussed later, many extraneous factors influenced the response to M&B 2050 so that the extent of blood pressure reduction was not completely uniform from one day to another. The improvement in predictability of response after M&B 2050 as compared with hexamethonium was one of degree, therefore, rather than being an absolute qualitative difference.

### Tolerance to M&B 2050

During one week of therapy with M&B 2050, administered subcutaneously twice daily to 10 hypertensive patients, there was no evidence of development of tolerance. In five of these listed in table 2 at the end of the week the mean effective dose of M&B 2050 was 0.5 times less (range −1.8 to +1.6 times) than the initial titrating dose. Five of these patients previously

had been under continuous therapy with hexamethonium for periods of 6 to 19 months. Review of their records showed that at the end of the first week of therapy with hexamethonium given subcutaneously, dosages had been raised progressively to a mean dose which was 1.9 times (range 1.5 to 2.5 times) the initial titrating dose. Thus, during this short period of observation the degree of tolerance induced by M&B 2050 administered subcutaneously was far less than that experienced previously with hexamethonium.

If oral administration was begun without any preceding period of parenteral therapy, there frequently was a transient hypotensive response lasting one to several days and occurring at a level considerably below the final effective maintenance dose. Following this, the increase in tolerance to the drug was very slight. For example, in 15 patients treated with oral M&B 2050 alone for periods varying from three to six weeks, the mean effective dose at the beginning of therapy was 232 mg. (range 45 to 518 mg.) per day of the ion; while at the end of the above period the average effective dosage was 275 mg. (range 135 to 562 mg.) per day.

### Cross Tolerance between M&B 2050 and Hexamethonium

The degree of cross tolerance existing between M&B 2050 and hexamethonium seemed to be very small. This was estimated in five patients who had been treated continuously with hexamethonium, subcutaneously administered for periods of six months to two years (table 2). When comparison is made between the initial effective dose of hexamethonium obtained by intravenous titration (prior to any previous therapy with ganglionic blocking agents) and the initial effective titrating dose of M&B 2050 (after prolonged therapy with hexamethonium) the data indicate that M&B 2050 was approximately 2.5 times more active (range 0 to 4 times) than hexamethonium. Thus, in these hexamethonium-treated patients, the relative potency of M&B 2050 was only half as great as in patients previously untreated with ganglionic blocking agents.

However, when comparison was made in these same patients between the initial titration dose of M&B 2050 and the dosage of hexamethonium required after prolonged therapy with the latter drug, the mean relative potency of M&B 2050 was 13.5 times (range 5 to 35 times) that of hexamethonium. It would appear, therefore, that the degree of cross tolerance between the two drugs is so slight that for practical clinical purposes one may consider that tolerance to hexamethonium does not induce significant tolerance to M&B 2050.

Table 2.—*Effect of Hexamethonium and Pentapyrrolidinium in the Same Patients Showing Development of Tolerance to Each and Degree of Cross Tolerance*

| Patient | Hexamethonium Ion, Effective Dose (mg.) | | | Pentapyrrolidinium Ion, Effective Dose (mg.) | |
|---|---|---|---|---|---|
| | Initial | After 1 wk. | After 6 to 18 mos. of treatment | Initial | After 1 wk. |
| A. S. | 8 | 12 | 20 | 2 | 1.5 |
| H. B. | 30 | 75 | 100 | 11 | 10 |
| C. P. | 2 | 4 | 75 | 1.8 | 3 |
| O. H. | 30 | 45 | 90 | 11 | 11 |
| J. C. | 50 | 100 | 120 | 20 | 11 |

### Factors Potentiating the Hypotensive Response to M&B 2050

Since the majority of the patients under treatment with M&B 2050 recorded their blood pressures at home, it was possible to study in some detail the various extraneous factors which influenced the blood pressure. These were as follows:

*Postural Effects.* (1) When the patient was up and about a smaller dosage usually was necessary to lower the blood pressure than when he was supine. Hence, a larger dose usually was required at bedtime. (2) Severe postural hypotension with faintness occurred more frequently after the morning dose than at other times. (3) Some of the patients noticed increased nocturia accompanied by decreased urinary frequency during the day.

*Additive Effects of Other Vasodilating Influences.* (1) The ingestion of alcohol frequently was followed by marked potentiation of the hypotensive action of M&B 2050. The amount

of alcohol need not be large since one or two "cocktails" was sufficient to induce significant additional reductions of blood pressure. (2) The ingestion of a large meal at times acted as a potentiating factor. (3) Vigorous exercise such as pushing a lawn mower was followed at times by an additional fall of blood pressure. This was in contrast to the untreated individual whose blood pressure usually increases with exercise. (4) During the hot summer weather the dosage of M&B 2050 frequently had to be reduced because of marked hypotension. The incidence of postural faintness or frank syncopal attacks increased at the onset of a period of unusually hot weather.

*Salt Depletion.* (1) When patients were placed on diets rigidly restricted in sodium the hypotensive effect of M&B 2050 was exaggerated. Such individuals became unusually susceptible to postural hypotension, while the margin widened between the level of blood pressure in the erect position as compared with the supine position. For this reason it seemed advantageous to permit a moderate salt intake in all of the noncardiac patients. In this way dosages could be raised to the point of influencing the supine pressure without inducing postural syncope. (2) Mercurial diuretics were administered at times to the cardiac patients in order to control the signs of congestive heart failure although the necessity for using them usually decreased greatly after the institution of hypotensive therapy. It was noted that as the edema accumulated the dosages of M&B 2050 became progressively less effective. However, immediately following the mercurial-induced diuresis marked reductions of blood pressure occurred. For this reason it was necessary in some instances to reduce the dosage of M&B 2050 for a day or two following the mercurial injection. (3) The potentiating action of hot weather described above may have been due in part to excessive salt loss.

## Therapeutic Results

Twenty-seven patients were treated with M&B 2050 orally as the sole medication for periods varying from two to six months. All could be classified as having severe, "fixed" hypertension. Twelve had grade IV hypertension with papilledema or had shown evidence of papilledema in the recent past (21 of the total group had received previous therapy with other drugs), nine had grade III and six had grade II hypertension.[9]

Dosages of the drug were administered as close to every eight hours as possible, the first dose being taken immediately after arising in the morning. Because of its long duration of action, the dosages of M&B 2050 should be widely spaced in order to avoid the additive effect of one dose overlapping on another.[6] Following the initial period of adjustment the mean daily effective dose was 300 mg. (range 135 to 630 mg.) of the ion. This was divided as follows: the average morning requirement was 95 mg., the afternoon dose 86 mg., and the mean bedtime dose was 122 mg. The larger dosage at night was well tolerated and usually was required to lower the blood pressure while the patient was in the supine position.

The results are based on the means of many home and clinic readings taken with the patient in the sitting position (table 3). Recordings taken with the patient in the supine position were somewhat higher, and those taken in the erect position were somewhat lower. The control value in each case was the level of blood pressure taken prior to any therapy after 48 hours or more of rest in bed in the hospital.

The average pretreatment blood pressure for the entire group was 230/135 (range 180/110 to 260/160) mm. Hg; the mean post-treatment

Table 3.—*Mean Reduction of Blood Pressure in 27 Hypertensive Patients Treated with Pentapyrrolidinium. Basis of Comparison Is Hospital Control Blood Pressure Prior to Any Form of Drug Therapy*

| Reduction of Blood Pressure | No. | % |
|---|---|---|
| *Systolic* | | |
| 60 mm. Hg or more | 15 | 55 |
| 40 mm. Hg or more | 22 | 81 |
| 20 mm. Hg or more | 26 | 96 |
| Less than 20 mm. Hg | 1 | 4 |
| *Diastolic* | | |
| 30 mm. Hg or more | 14 | 52 |
| 20 mm. Hg or more | 23 | 85 |
| 15 mm. Hg or more | 24 | 89 |
| Less than 15 mm. Hg | 3 | 11 |

blood pressure was 170/110 (range 130/95 to 210/130) mm. Hg. Slightly more than 50 per cent of the patients exhibited a reduction of 60 mm. Hg or more in systolic pressure and of 30 mm. Hg or more in the diastolic pressure. Twenty-two, or 81 per cent, showed systolic reductions of 40 mm. Hg or more and 23, or 85 per cent exhibited diastolic reductions of 20 mm. Hg or more.

The hypotensive response to M&B 2050 was somewhat more predictable than the response to hexamethonium and once a maintenance dosage level had been established, the necessity for constantly modifying it was not nearly as great. Nevertheless, variability produced by the extraneous additive factors previously discussed or by unknown causes was sufficient to be an ever-present potential source of inconvenience and even hazard to many patients.

For example, patient C. P., a 42 year old, white, male teacher with "malignant" hypertension in therapeutic remission was taking 3 doses per day of 100, 150 and 350 mg. of M&B 2050 in the morning, afternoon and at bedtime, respectively. On arising in the morning his blood pressure usually was 190/110 mm. Hg; this fell after the morning dose to 140/95 mm. Hg. It then rose gradually to 190/120 mm. Hg at 2 p.m. but fell again after the 2 p.m. dose to 160/110 mm. Hg. During the evening the blood pressure rose gradually to 190/120 mm. Hg. Two hours after his morning dose on a hot July day he walked up a steep hill to the hospital for his regular office visit. When he appeared in the clinic he was pale and on the verge of syncope. His blood pressure sitting in a chair was 90/75 mm. Hg. Immediately after lying down the pressure rose to 165/115 mm. Hg, and after resting supine for an hour the patient was able to go about his usual day's activities.

TABLE 4.—*Incidence of Side Effects Produced by Pentapyrrolidinium in 27 Hypertensive Patients*

| Side Effect | No. | % |
|---|---|---|
| Impaired visual accommodation | 14 | 52 |
| Dry mouth | 12 | 40 |
| Constipation of any degree | 11 | 40 |
| Not controlled by neostygmine | 4 | 15 |
| Enemas required | 0 | 0 |
| Postural faintness | 8 | 30 |
| Postural syncope | 1 | 4 |
| Impotence | 8 | 30 |

### SIDE EFFECTS

The so-called side effects of M&B 2050 were similar to those experienced with hexamethonium; all could be accounted for on the basis of ganglionic blockade. The most prominent of these were postural faintness, dry mouth and loss of visual accommodation (table 4). These side effects were most pronounced when the blood pressure was the lowest. Many of the patients required reading glasses with positive lenses for occupations requiring accommodation for near vision and tinted glasses to wear in bright sunlight because of the failure of pupillary constriction.

In contrast to the lack of constipation in patients treated with parenteral M&B 2050, oral ingestion of the drug was accompanied by some degree of constipation in many instances (table 4). It was not as severe as that observed in patients taking hexamethonium and in most instances responded to oral neostigmine in doses of 15 to 45 mg. In a few instances irritant cathartics also were necessary. Paralytic ileus and severe obstipation did not occur. One of the patients who suffered severe bouts of acute gastric dilatation when taking parenteral hexamethonium suffered a similar attack on oral M&B 2050.

Impotence was a frequent and troublesome side effect in the male. In general the middle aged and elderly patients suffered complete impotence during the entire period of treatment whereas most of the younger patients were only partially incapacitated. The urethane of $\beta$-methylcholine (Urecholine), 10 mg. under the tongue every hour for three hours preceding sexual intercourse, seemed to benefit some of the patients, but it is impossible to say whether the effect of Urecholine was real or psychogenic.

A few patients complained of chilly sensations in a cold environment probably due to failure of reflex vasoconstriction in the skin. This required that they dress warmly during

cooler weather in order to conserve body heat. None of the patients taking M&B 2050 suffered from inability to empty the urinary bladder; one of these patients had been unable to take hexamethonium because of this side effect.

Certain side reactions, particularly dryness of the mouth and frequent postural faintness, were most prominent during the early stages of treatment but tended to diminish as treatment progressed, whereas other side effects such as impotence remained unchanged during the entire period of treatment.

## Discussion

The purposes of this study were twofold: to determine, first, whether M&B 2050 possessed therapeutic advantages over hexamethonium and, second, whether it could be given safely and effectively by the oral route of administration. Our findings in general are in agreement with those of Smirk.[6] In regard to the first question M&B 2050 appeared to be superior to hexamethonium in several respects:

1. The degree of tolerance induced by M&B 2050 definitely was less than that observed with hexamethonium. The negligible degree of cross tolerance was of theoretic as well as of practical importance. The reason for the development of "tolerance" to the hypotensive effects of hexamethonium has not been clear. It was unknown whether this represented a true drug tolerance or whether, despite continued ganglionic blockade, some other hypertensive mechanism operating humorally, or in some other way not dependent upon transmission of impulses through automatic ganglia, had been activated to restore the hypertension. The fact that after the development of tolerance to hexamethonium the patients remained sensitive to relatively small doses of M&B 2050 suggests strongly that the resistance to hexamethonium represented true drug tolerance. From the practical point of view the lesser degree of tolerance experienced with M&B 2050 permitted management of the patient with less frequent need for dosage readjustment.

2. When compared with hexamethonium, the duration of action of pentapyrrolidinium was longer than that of hexamethonium and permitted less frequent administration.

3. The response following oral administration of M&B 2050 was more predictable than that observed after hexamethonium. The effective dosage range was not as wide and the variations of blood pressure response on a given dose from day to day not as great. The greater predictability of response may have been related at least in part to the lesser effect of M&B 2050 on intestinal motility than that produced by hexamethonium. The degree of constipation and stasis in the gastrointestinal tract produced by oral M&B 2050 could be controlled usually by simple measures such as the administration of oral neostygmine. As a result accumulation of the drug in the gut seldom occurred. In the case of oral hexamethonium such accumulation of the drug may be followed by absorption of large dosages over a long period of time leading to severe and persistent hypotensive reactions. Although syncopal attacks occurred after M&B 2050, the prolonged collapse reactions often accompanied by ileus were not seen as they had been with hexamethonium.

Nevertheless, oral therapy with M&B 2050 left much to be desired. Some of the patients were controlled, with minimal side effects, but in the majority critical dosage adjustment was required, slight excesses producing hypotensive reactions and slight under-dosage failing to induce a significant hypotensive response. In addition, in order to lower the blood pressure, it usually was necessary to elevate dosage to a point where side effects were frequent particularly during the early weeks of adjustment.

During the treatment period it was observed frequently that vasodilator influences such as heat, alcohol, exercise and food, which ordinarily would have no effect on blood pressure, produced a significant hypotensive effect in the patient treated with M&B 2050. Under normal conditions such vasodilator influences are opposed immediately by homeostatic vasoconstrictor responses mediated over the sympathetic nervous system. These reflexes produce vasoconstriction in other vascular areas thereby preventing any appreciable fall in total peripheral vascular resistance. However, M&B

2050, by producing ganglionic blockade, prevents these homeostatic adjustments. Therefore vasodilation in one vascular area will be unopposed by vasoconstriction in other regions, and, if the dilated area is large, the systemic blood pressure will fall. These considerations provide a rational basis for combining the ganglionic blocking agents with other vasodilating drugs. The effects of combining pentapyrrolidinium with other hypotensive agents will be discussed in a succeeding paper.[10]

## Summary and Conclusions

1. Comparisons were made between the effects of hexamethonium and pentapyrrolidinium (M&B 2050) in hypertensive patients. The following differences were noted: (a) M&B 2050 was approximately five times more potent than hexamethonium. (b) The duration of the hypotensive effect was 40 per cent longer. (c) Less tolerance occurred after M&B 2050. Cross tolerance between this drug and hexamethonium was very slight. (d) Less constipation was produced by M&B 2050 and there was no interference with emptying of the urinary bladder. The constipation could be controlled with oral neostygmine and/or irritant cathartics. (e) On oral administration a more predictable hypotensive response was obtained.

2. The other side effects of ganglionic blockade were similar to those observed with hexamethonium.

3. Various extraneous factors such as postural changes, ingestion of alcohol or a heavy meal, exercise, hot weather and salt depletion intensified the hypotensive effect of M&B 2050.

4. Unlike hexamethonium it was possible to lower the blood pressure significantly in the majority of patients with oral administration of M&B 2050 without producing prolonged collapse reactions or paralytic ileus. However, critical adjustment of dosage was necessary and side effects were not infrequent, the most disturbing being postural faintness and impotence. For these reasons M&B 2050 seems to be of greatest value in those cases of severe hypertension which cannot be controlled by simpler measures.

## Sumario Español

El nuevo agente bloqueador ganglionar, pentapyrrolidinium o M&B 2050 aparenta tener ciertas ventajas distinctivas sobre el hexamethonium en el tratamiento de la hipertensión severa. Estas ventajas incluyen una acción más prolongada, mayor potencia, menor tolerancia, menos interferencia con la movilidad intestinal y mas importante aún, una respuesta mas uniforme de día en día a la administración oral. Sinembargo, un ajuste crítico de la posología fué necesario y los efectos no deseables no fueron infrequentes, el más alarmante siendo el desfallecimiento postural y la impotencia.

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# Arterial Supply to the Nodal Tissue in the Dog Heart

*By* MYRON H. HALPERN, PH.D.

A study of the hearts of 107 dogs revealed that the blood supply to the sinoatrial node was from three sources: right coronary artery, left coronary artery, and right internal mammary artery. A dominant pattern of supply was found in 90 hearts. Three variations are described. The importance of arterial anastomoses to the sinus node and their role in the formation of an extracardiac coronary arterial system are discussed.

THE sinoatrial and atrioventricular nodes have been under investigation from many aspects, anatomic as well as physiologic. Many of these studies have been carried out on the dog, since it is the laboratory animal most commonly used in experimental procedures. The pattern of blood supply to the sinoatrial node in the dog has been described by Meek, Keenan and Theisen,[1] Moore,[2] Pianetto,[3] and Kazzaz and Shanklin.[4] Though there is general agreement as to which vessels of the coronary tree supply the sinoatrial node, the present author has found that the coronary system is not the only source of blood supply to this region. In the light of recent investigations on the sinoatrial node in other mammals (mouse, Nomura[5], and rat, Halpern[6]) it might be expected that vessels from noncardiac sources would anastomose with the vessels that supply the sinoatrial node in the dog.

The purpose of this work is to point out the anastomotic connections, their extent, and their relations to the arterial supply of the sinus node region.

## MATERIAL AND METHODS

For this study, the coronary arteries of 107 dog hearts were injected with latex, vinyl acetate, or nylon. Most of the animals were obtained from student laboratories in physiology and pharmacology, and nothing is known of their breed or age. However a few dogs that were obtained from other sources were of known age, ranging from newborn to 14 years.

In each heart the right coronary artery was injected with a red mass while the left coronary artery was injected with a blue mass. The isolated hearts were cleared either by the glycerine technic or by a modified Spalteholz method. All hearts were treated the same except where noted. The hearts were removed while beating and were placed immediately in warm saline containing 2 per cent each of magnesium sulfate and sodium citrate. After cessation of beating, the hearts were placed in fresh solution and refrigerated until rigor mortis passed. They were then flushed with tap water until the washings were clear. At this time the hearts to be injected with latex were filled by injecting each coronary artery separately through its origin from the aorta. A drop of concentrated hydrochloric acid was placed on this point after removal of the cannula. The acid coagulated and set the latex. After adequate fixation in 70 per cent alcohol acidified with hydrochloric acid, these hearts were transferred to fresh 70 per cent alcohol.

The vinyl acetate specimens, after washing with tap water, were flushed with acetone. The coronary arteries were then dried by blowing a gentle stream of compressed air (6 pounds pressure) through the vessels. Ethyl acetate was injected and the vessels dried again with compressed air. This was followed by the vinyl acetate injection, the procedure was the same as with the latex except that the plastic was set with water. These specimens were fixed in 70 per cent alcohol.

Those hearts to be injected with nylon were flushed with 70 per cent alcohol after tap water. The injection mass was prepared by dissolving nylon in hot 80 per cent ethanol until it had the consistency of cream. The mass was injected while hot and then hardened in cold water. Fixation was in 70 per cent alcohol, which did not affect the nylon once it had set.

After fixation in 70 per cent alcohol, all hearts were placed in a glycerine-potassium hydroxide clearing solution (20 per cent glycerine, 2 per cent

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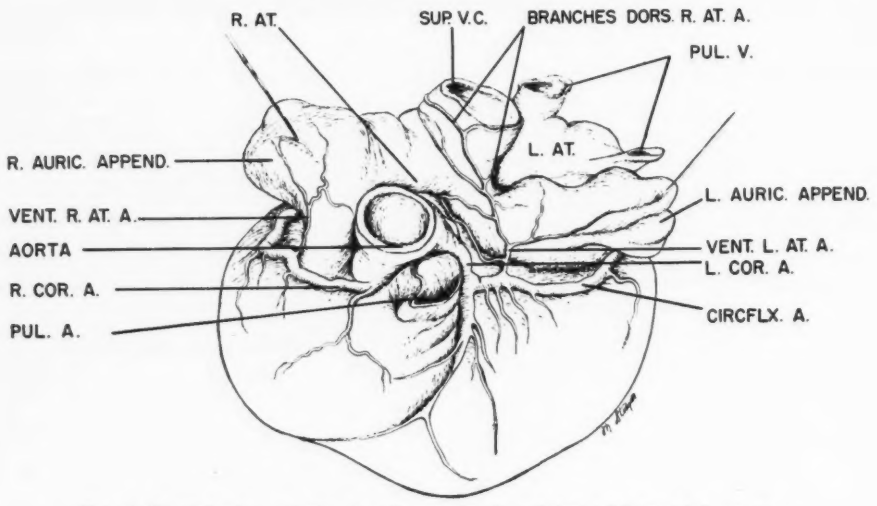


FIG. 1. Cranial view of the dog heart showing right and left atrial arteries.

potassium hydroxide) until the tissues became jelly-like. Transfer was made to 70 per cent alcohol to which a few milliliters of hydrogen peroxide were added to bleach the remaining blood pigments. This bleaching-hardening solution was changed at frequent intervals. When the hearts were bleached, they were transferred to 95 per cent alcohol. After several days, a change was made to absolute alcohol except for the latex injected specimens. These were placed in a mixture of three parts 95 per cent alcohol and one part glycerine for a week. This mixture was replaced by one of equal parts alcohol and glycerine. After a week, a change was made into 1 part alcohol-3 parts glycerine mixture for final clearing. The specimens were stored in pure glycerine.

From absolute alcohol, the vinyl plastic and nylon hearts were carried into benzene. They remained here until cleared, changing the benzene whenever murky. The vinyl hearts were transferred to a mixture of one part toluene and three parts benzyl benzoate for final clearing and storage. Methyl salicylate should be avoided for it tends to dissolve the vinyl plastic. The nylon hearts, however, were placed in methyl salicylate from benzene. They may be stored here indefinitely. In six of the animals, the hearts remained in the thorax and the entire chest was injected with latex. These specimens were carefully dissected.

An additional six hearts from newborn pups were fixed in Bouin's fixative and serially sectioned. Two of these hearts were stained with Goldner's[7] modification of Masson's technic; four of the hearts were stained with hematoxylin and eosin.

## OBSERVATIONS

Careful examination of 107 dog hearts by means of dissection and clearing reveals a dominant pattern of blood supply to the sino-atrial node. The right coronary artery gives off three major right atrial arteries: a ventral right atrial artery, an intermediate right atrial artery, and a dorsal right atrial artery. The ventral right atrial artery is the first large atrial branch arising from the right coronary artery under cover of the auricle. This vessel passes to the deep surface (aortic side) of the right auricle where it ramifies to supply this structure (fig. 1).

The intermediate right atrial artery arises from that portion of the right coronary artery coursing around the lateral part of the heart in the atrioventricular sulcus (fig. 2). This atrial branch begins at a point opposite the junction of the right auricle with the right atrium. It continues onto the lateral surface of the right atrium, dorsal to the junction of the atrium with its appendage, and its terminal branches spread over the lateral portion of the right atrium. Some branches extend onto the external surface of the auricle (fig. 2).

The dorsal right atrial artery is the last significant atrial branch from the right coronary artery. This vessel arises from the right coronary artery ventral to the point of junction of the inferior vena cava with the right atrium. It curves over the dorsal and lateral parts of the right atrium giving off branches in course (fig. 2). Reaching the dorsal portion of the right

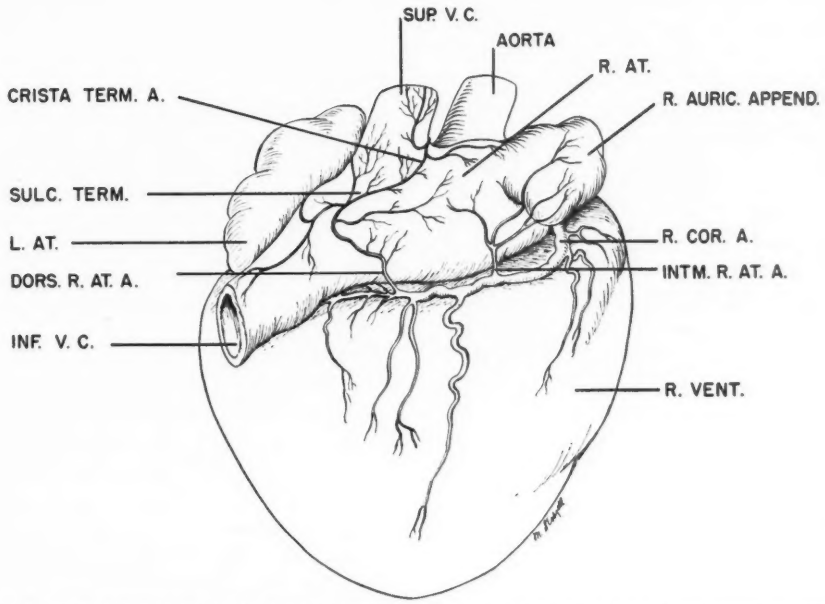


FIG. 2. Right lateral view of the dog heart showing the atrial branches of the right coronary artery.

atrium it runs to the sulcus terminalis where it penetrates the epicardial tissue to run lengthwise through the crista terminalis, as shown in microscopic section (fig. 3). This portion of the dorsal right atrial artery, coursing through the crista terminalis, is known as the cristal branch. Before the dorsal right atrial artery goes deep to become the cristal artery, it gives off several branches some of which pass caudally along the inferior vena cava. Others run dorsally to go into the interatrial septum or ramify over the dorsal parts of the right and left atria. From the cristal artery, branches ascend along the superior vena cava, others proceed around the caval funnel to reach the aortic surface of the right atrium, while still others pass onto the cranial portion of the right auricle (figs. 1 and 2).

The cristal artery and its branches, on and around the superior vena cava, are of considerable importance in the blood supply to the sinoatrial node. These will be discussed in more detail below.

The left coronary artery gives off left atrial arteries which correspond to those named on the right. These vessels have been described and figured by Meek, Keenan and Theisen.[1]

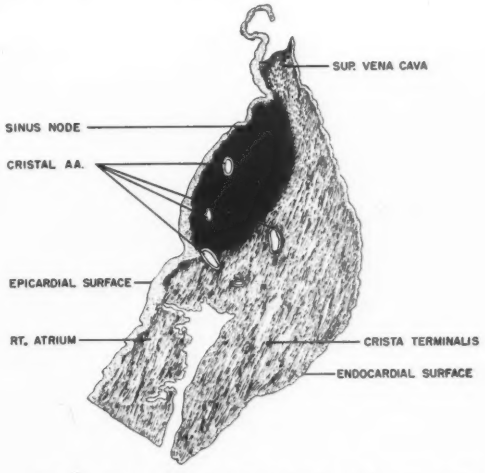


FIG. 3. Projection drawing of a frontal section of a pup heart through the superior vena cava and right atrium. The head of the sinus node is shown at the auriculocaval junction.

Since there are no differences in the present series, the reader is referred to the earlier work. However, the ventral left atrial artery is of importance in the present investigation. As described by the above authors, it originates from the circumflex branch of the left coronary

artery. The stem of origin almost immediately breaks up into many branches (fig. 1). Several branches ramify over the undersurface (aortic face) of the left auricle. A single branch runs deep in the sulcus between atria and aorta whence it turns deep to send branches into the base of the interatrial septum and tissue of that region. The main branch of the ventral left atrial artery passes to the right across the aortic face of the left and right atria (fig. 1). It veers toward the superior vena cava where its branches anastomose with those from the dorsal right atrial artery (cristal branch) that passed around the caval funnel (fig. 1). These points of anastomoses are easily demonstrated since the vessels from the right coronary artery have a red mass in them and those from the left coronary have a blue mass in them. The site where these two colors fuse is taken to be the point of anastomosis.

The location of the sinoatrial node in the dog has been described as lying at the junction of the superior vena cava and right auricle.[8, 9] It lies lengthwise in the sulcus terminalis on the caval side of the crista terminalis (fig. 3). Its head is at the auriculocaval junction and its tapering tail extends almost to the inferior vena cava. The blood supply to this region is by the cristal artery, a branch of the dorsal right atrial artery. However, this simple pattern is not the complete picture. There are important anastomoses that probably account for a large share of the blood supply. In 90 of the 107 hearts studied, the cristal artery is a branch of the dorsal right atrial artery (fig. 5*A*). This branch supplies the crista terminalis and neighboring area, it also supplies the sinus node (fig. 3) as demonstrated by serial microscopic sections. On the ventral wall of the right atrium, visible anastomoses occur between the dorsal right atrial artery and ventral left atrial artery.

Mention has been made of branches from the cristal artery that ascend on the superior vena cava. In order to check the extent of these ascending vessels, the intact thorax was dissected in six dogs. Most of the ascending ves-

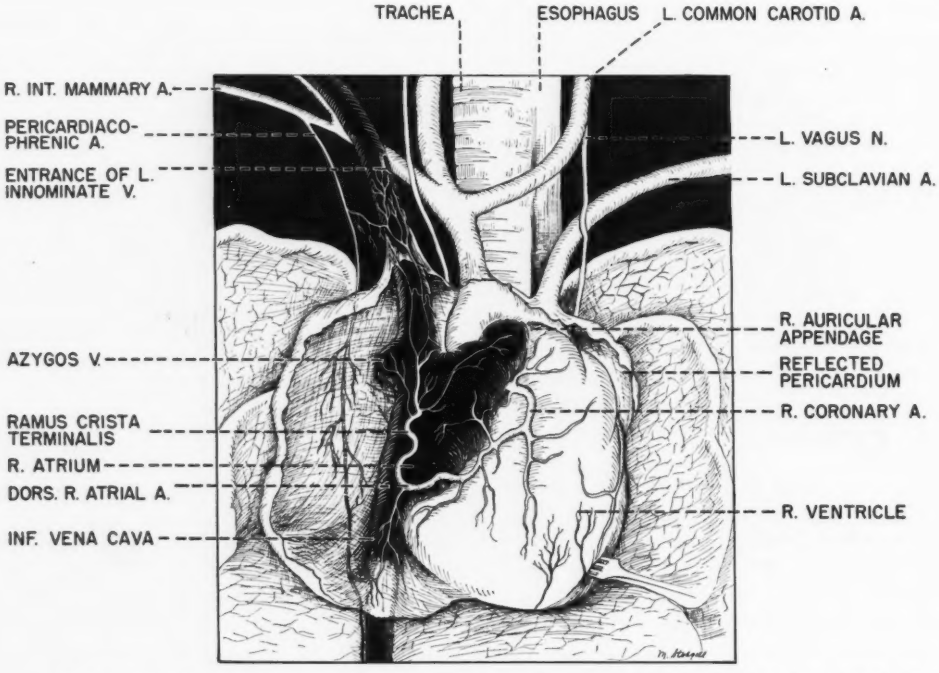


FIG. 4. Right lateral view of the dog heart within the thorax. The pericardium is reflected to show the extent of the extracardiac arterial anastomoses.

sels, as well as the descending branches found on the inferior vena cava, are vasa vasorum to the caval veins. But some of these vessels anastomose with pericardial arteries. In addition to these, in the region of the middle one third of the superior vena cava, small branches from the right pericardiacophrenic artery extend onto the superior vena cava to anastomose with some of the ascending vessels (fig. 4). These anastomotic connections between the right pericardiacophrenic artery and the ascending branches of the cristal artery together form an extracardiac (collateral) coronary arterial system. The ascending portion of the cristal artery is seen in all hearts studied, but the extracardiac anastomoses with the branch from the right internal mammary artery is seen only in the dissected thorax with the heart injected in situ.

The cristal artery is not always a branch of the dorsal right atrial artery as depicted in figure 5*A*. In some instances, the cristal artery is of dual origin. (1) The portion of the crista terminalis at the auriculocaval junction and the head of the sinus node are supplied by a branch of the ventral left atrial artery. (2) The portion of the crista near the inferior vena cava and the tail of the sinoatrial node are supplied

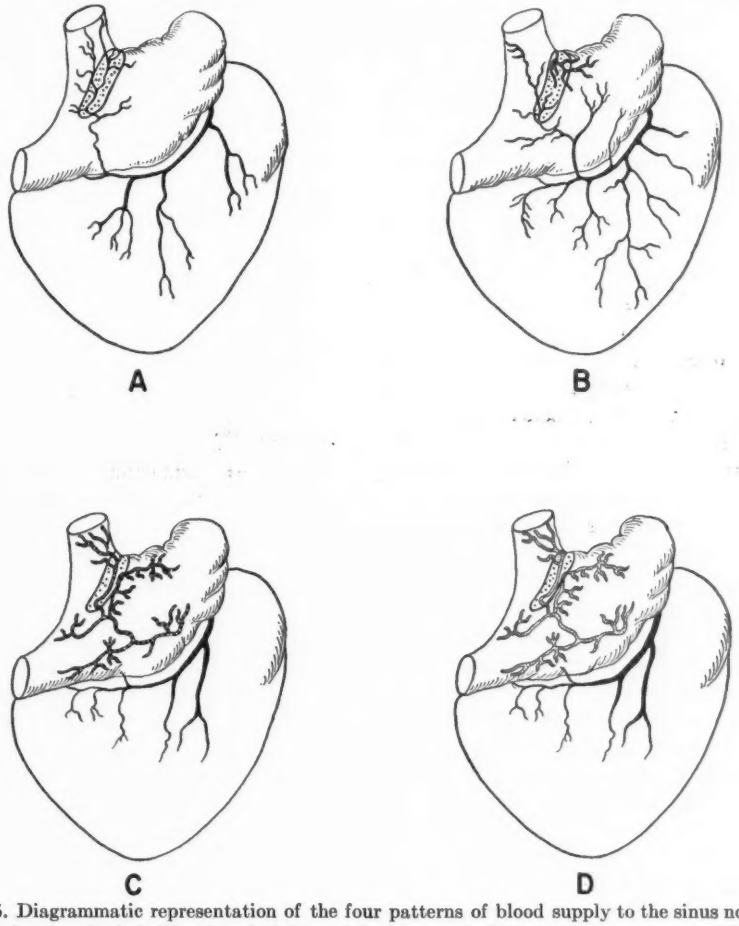


FIG. 5. Diagrammatic representation of the four patterns of blood supply to the sinus node. The nodal region is stippled. The dorsal right atrial artery and right coronary artery are black, the ventral left atrial artery has alternating black and white blocks, the ventral right atrial artery is in fine stipple.

by a branch from the dorsal right atrial artery (fig. 5*B*). This configuration was found in six hearts of the 107 examined. When this pattern occurred, the ascending branches on the superior vena cava came from that part of the cristal artery which supplied the head of the node, that is, from the ventral left atrial artery.

In other instances, the dorsal right atrial artery is reduced or missing. When present in the reduced form it supplies a small caudal portion of the dorsolateral wall of the right atrium close to the atrioventricular sulcus. The cristal artery is then formed entirely from the ventral left atrial artery (fig. 5*C*). The ventral left atrial vessel coursed through the notch formed by the superior caval vein and the right atrium. It then proceeded deep in the sulcus terminalis to become the cristal branch. The crista terminalis and the sinus node were thus supplied by this vessel (fig. 5*C*). This arrangement has been seen in 10 of the 107 hearts. No anastomotic connections were found with the dorsal right atrial artery in this case. The ascending cristal branches were present but were derived from the ventral left atrial artery.

In one isolated case out of 107, the cristal artery was formed by the ventral right atrial artery. This vessel extended across the ventral wall of the right atrium, passed around the caval funnel and ramified over the lateral surface of the right atrium (fig. 5*D*). The dorsal right atrial artery was poorly developed.

The sinoatrial node has an extensive blood supply from many sources as a result of the abundant anastomoses between vessels. The right coronary artery (via the dorsal right atrial branch), the left coronary artery (via the ventral left atrial branch), and the right internal mammary artery (via the pericardiacophrenic anastomoses upon the superior vena cava) all contribute to the vascularization of the crista terminalis region and to the blood supply of the sinus node.

## Discussion and Conclusions

These observations on the distribution of blood vessels to the sinus node are in substantial agreement with the views of other workers. In the present investigation, the blood supply to the atrioventricular node has been purposely deemphasized at this time. No discrete set of vessels specific to this node has been observed. However, the atrioventricular blood supply seems to be by those atrial branches of the right and left coronary arteries that pass into the interatrial septum. Moore[2] noted that the A-V node is supplied by branches of the right and left atrial arteries. Haas and Kalm, quoted in Condorelli's[10] work, stated that a small branch from the circumflex left coronary artery nourishes the atrioventricular node and the bundle of His. The septal branch of the left coronary artery which runs in the interventricular septum sends twigs which also supply parts of the interatrial septum. The septal artery and its branches have been described by Moore[2] and Pianetto.[3] Pianetto[3] stated that all of the atrioventricular conduction system could receive its blood supply from the septal artery. Glomset and Glomset[8] stated that a "good-sized artery" runs through the atrioventricular node in the dog. It was a branch of the septal artery. Nonidez[9] in his figure 1*B* showed a vessel passing through the A-V node of the pup which was labelled the "nodal artery." Copenhaver and Truex[11] stated that the A-V nodal region lacks a recognized nodal artery but contains arterioles and venous sinusoids.

The anastomotic connections between the vessels that supply the sinus node are of interest. These connections introduce the problem of extracardiac coronary arteries and collateral circulation of the heart. The fact that there exists an extracardiac coronary arterial system was first recognized in the rat. Cardiac veins that drained the heart to an extracardiac site were described by Halpern[12] who illustrated extracardiac coronary arteries without labelling them. Additional investigations on the coronary arteries of the rat revealed that the extracardiac coronary arteries supplied nodal tissue.[6] In the mouse, Nomura[5] noted a vessel from the right subclavian artery that supplied the sinoatrial node. The relationship of this vessel to the node in the mouse was similar to that of the cristal artery to the sinus node in the dog. The anastomosis between the pericardiacophrenic artery and the ascending branches of the cristal artery forms an extracardiac coro-

nary system. If the extracardiac coronary arteries, as occur in rat and mouse, are a primitive characteristic a similar condition is retained in the dog as illustrated in figure 5. This system is augmented by anastomoses between pericardial arteries and other branches of the dorsal right atrial artery. No difficulty was encountered in filling these vessels with the injection mass.

The concept of the persistence of an extracardiac source of blood supply to the heart is important in the light of the current attempts at revascularization of the heart by cardiopericardiopexy.[13-17] It is the aim of this procedure to establish a collateral (extracardiac) circulation to the heart. Such a circulation exists normally in the dog. The extent of such an extracardiac coronary system in the normal heart of man remains unknown. Such investigations on the human heart are now in progress by the author.

The amount of blood that collateral vessels carry to the heart of the dog is not known. The presence of extensive anastomoses between the right and left coronary arteries indicates a vast blood supply to the sinus node. This observation also indicates that there is little possibility of vascular occlusions affecting the sinoatrial node. This idea was also advanced by Meek, Keenan and Theisen[1] who stated that "the sinus node is furnished with an abundant and sure blood supply," and that it is "extremely difficult to reduce its circulation sufficiently to cause injury. Likewise auricular (atrial) thrombi are seldom if ever found in the region of the sulcus terminalis. The explanation for both facts is readily found in the anastomosing blood supply." Moore[2] found it impossible to delineate definite areas of blood supply in the atria because of the abundant anastomoses. He pointed out that though the sinus node receives its blood supply from the right distal atrial artery (dorsal right atrial artery), there is, however, abundant anastomoses with other atrial arteries. In his series, Moore observed the injection mass to flow from the left coronary artery to the right coronary artery through the anastomoses between the right and left atrial vessels. In the horse Sabathie and Pianetto[18] found that the sinus node had a double blood supply: from the left circumflex and right coronary arteries. From these facts, it may be stated with assurance that occlusive vascular changes are of little consequence in affecting the sinus node in its role as pacemaker of the heart. In experimental procedures on the sinus node, cognizance should be taken of the fact that the node and its blood supply form an intimate morphologic unit.

## Summary

1. Examination of 107 dog hearts revealed that the sinoatrial node received a blood supply from three sources; right coronary artery, left coronary artery, and right internal mammary artery.

2. A dominant pattern of supply was found in 90 hearts. Three variations in the pattern were described and the incidence of each was noted.

3. The importance of the arterial anastomotic connections to the sinus node is discussed. These anastomoses form an extracardiac coronary arterial system. The implications of this system are described.

## Sumario Español

1. Examen de 107 corazones caninos reveló que el nódulo sinuoauricular recibe su circulación sanguínea de tres fuentes; la arteria coronaria derecha, la arteria coronaria izquierda y la arteria mamaria interna derecha.

2. Un patrón dominante de abastecimiento se encontró en 90 de los corazones. Tres variaciones del patrón fueron descritas y la incidencia de cada una se notó.

3. La importancia de las conecciones anastomóticas arteriales al nódulo sinuoauricular se discuten. Estas anastomosis forman un sistema arterial coronario extracardíaco. Las implicaciones de este sistema se describen.

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# The Construction of Mean Spatial Vectors From Null Contours

*By* Ernest Frank, Ph.D., and Calvin F. Kay, M.D.

Experimental and theoretic evidence reveal substantial errors in the determination of mean heart vector orientations exclusively from null contours. Over the limited range of orientations studied, the mean heart vector angle determined by the perpendicular-plane construction departs by as much as 17 degrees from the true angle. These sizable construction errors, strongly dependent upon such factors as heart position and medium shape, are superimposed upon other errors inherent in the many assumptions made in electrocardiographic field analysis.

IT would appear self-evident upon examining the history of progress in such fields as biology, biophysics, physical science and others, that methods of electrocardiography which have a firm theoretic foundation based upon known physical laws will ultimately grow to a stature beyond any semiempiric methods. It is in this spirit that a variety of quantitative experiments are being conducted in this laboratory in an attempt to establish a sound experimental and theoretic basis for the analysis of the relationship between the electric currents generated by the heart and the concomitant electric potential differences produced on the surface of the human subject.

In the course of some of these studies it became necessary to develop an accurate technic[1] to measure boundary potentials on the surface of volume conductors with respect to the midpotential of an immersed current dipole. This technic utilizes, in part, a cylindric conductor as a standardizing tank. While this apparatus was designed primarily for torso-model studies, it became obvious that a convenient side pursuit would be the investigation of the validity of the perpendicular-plane construction used in connection with mean spatial vectors and null contours on the human subject. It is the purpose of this paper to present some of the results of this investigation.

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## Null Contours and Mean Spatial Vectors

Studies of the potential differences between the Wilson central terminal and an exploring electrode placed at a variety of positions on the human subject have led to the definitions and use of three zones on the body surface.[2] A schematic representation of these three zones is illustrated in figure 1 for the case of the QRS complex. The negative zone is defined as that portion of the surface of the human subject where the net area under the QRS complex is negative; the positive zone is defined as the surface where the net area under the QRS complex is positive; the border between these two has been called the transitional zone where the net area under the QRS complex is zero. The same definitions of the three zones are used for the P and T waves, and each wave generally has a different transitional zone. In many human subjects the transitional zones are fairly smoothly shaped bands, approximately elliptical in shape. However, in some cases the transitional zones are highly irregular.[3]

Various methods of analysis utilizing the transitional zones have been proposed.[4-9] The foundations and assumptions of most of these methods are similar. In essence they amount to plotting the transitional zone as a loop,

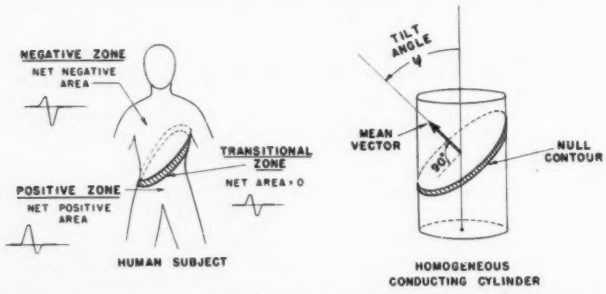


FIG. 1. The negative, positive and transitional zones on the surface of a human subject are illustrated at the left for the case of the QRS complex. A homogeneous conducting cylinder representing the human torso is shown at the right in which a mean vector located on the cylinder axis is drawn perpendicular to the plane containing the null contour tilted at an angle $\psi$ with respect to the cylinder axis. The sense of the mean vector has been reversed from the usual convention to clarify this illustration.

called the null contour, on a cylinder of dimensions comparable to those of the human subject as indicated in figure 1. The cylinder is regarded as a rough approximation of the human torso shape, and it is assumed to be a homogeneous volume conductor. A mean manifest heart vector positioned on the axis of the cylinder is postulated to represent the electrical activity of the heart. It is asserted that the orientation of this mean vector is perpendicular to the plane which passes (most closely) through the null contour, the potential of which is assumed to be equal to the mid-potential of the mean vector (dipole). In this way the null contour is associated with the orientations in three dimensions of P, QRS and T mean vectors.* The angles between these vectors are being investigated with the hope of correlating them with heart disorders.

This method of exploring the relationship between the electric activity of the heart and the potentials it produces on the body surface involves many approximations some of which are known to be considerably in error. For example, the Wilson central-terminal voltage, assumed here to remain constant, is believed to vary by sizeable amounts during the cardiac cycle[10, 11, 12] and this has a very pronounced effect on the location of the transitional zone and, hence, on the mean vector orientation determined from it. Also the representation of the human torso by a cylinder may not be sufficiently accurate for precise work. Furthermore, it has not been established that the human torso can be regarded as a homogeneous conducting medium so far as heart currents are concerned.[13] In addition, the physical significance of the mean heart vector and its correlation (by some sort of complicated integration) with the more firmly based manifest heart vector which changes its orientation and moment at an irregular rate during the heart beat is obscure. Finally, the perpendicular-plane construction involves considerable error in the determination of the orientation of the mean heart vector. This last defect is the subject of this paper and can be seen to be only one small aspect of the entire problem.

* Additional mean vectors using smaller time intervals also have been defined; for example, the 0.04 second QRS vector.

## PERPENDICULAR-PLANE CONSTRUCTION

It can be seen readily in qualitative terms that the perpendicular-plane construction cannot be correct from a brief examination of a physical system consisting of a current dipole, representing the mean heart vector, located on the axis of a homogeneous conducting cylinder. The dipole produces a current field in the cylinder indicated in figure 2. Since the medium outside the cylinder is a perfect insulator, all the current is confined to the cylinder. This means that the current lines at the wall of the cylinder must be tangent to the cylinder wall. Since isopotentials are everywhere perpendicular to current lines in such a physical system, it becomes obvious

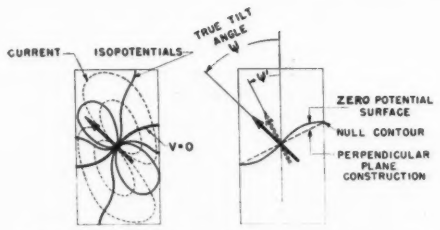


FIG. 2. Current lines (dashed) and isopotentials are shown at the left in cross section for a homogeneous conducting cylinder in which is immersed a centric current dipole. The isopotential surface, $V = 0$, which is not a plane surface, is seen to meet the cylinder wall at right angles as do all other boundary isopotentials. The error entailed in the perpendicular-plane construction is indicated on the right which is drawn approximately to scale. See text for discussion.

that all boundary isopotentials must meet the cylinder wall at right angles. The zero-potential surface $V = 0$ which is the dipole midpotential, is no exception to this general physical principle. For distances from the dipole that are very small in comparison with the cylinder radius, the surface $V = 0$ does coincide with a plane perpendicular to and passing through the center of the dipole. (This plane does not pass through the null contour.) However, as the boundary is approached the surface, $V = 0$, must curve away from this plane in order to become perpendicular to the cylinder wall. Thus, it can be seen qualitatively that the perpendicular-plane construction must be in error, and further that the zero-potential surface within the cylinder is not a plane, as has been assumed by others.

The meaning in terms of dipole orientation of this behavior of the zero-potential surface is illustrated in figure 2 which shows a dipole tilted at an angle, $\psi$, with respect to the cylinder axis. The zero-potential surface, which is S-shaped in cross section, associated with the dipole establishes the null contour on the cylinder wall. The perpendicular-plane construction, indicated by the dashed line through the null contour, leads to an apparent tilt angle, $\psi'$ (of the dashed vector drawn perpendicular to the plane through the null contour), which is smaller than the true tilt angle of the dipole that produced this null contour. The discrepancy between the true and apparent orientations is seen to be very sizeable in figure 2 which is drawn approximately to scale. Quantitative measurements of the actual size of the errors entailed in this construction have been made with the apparatus and method described below.

## EXPERIMENTAL METHOD

The location of the zero-potential contour on the wall of a homogeneous conducting cylinder as produced by a finite dipole* was studied experimentally for both centric and eccentric dipoles. The basic method used is described elsewhere along with some of the design problems.[1] A description of the experimental arrangement can be given with reference to figure 3. The finite dipole, consisting of two ¾ inch-radius nickel discs separated by a small 5/16 inch insulating spacer, is immersed in a tap-water† filled plexiglass cylinder of 7 inches radius and 30 inches length by means of an insulated rod containing current leads. The dipole can be positioned (by the assembly shown which is equipped with various scales and dials) in depth of immersion and distance from the cylinder axis. The dipole orientation is adjusted by a pivot at the bottom of the supporting rod, and also by twisting the rod about its axis. A potential difference is applied to the dipole through a resistance-capacitance bridge and the dipole current I is distributed throughout the cylinder. The bridge detector, connected between watertight pick-up electrodes on the cylinder wall and the junction between the bridge resistors $R_1$ and $R_2$, consists of a 40-decibel preamplifier in cascade with a harmonic wave analyzer tuned to the operating frequency of 1000 cycles per second.‡ Complete shielding, not shown in figure 3, is employed throughout.

The ground side of the detector is established at

* A finite dipole is defined as a current source and sink separated by a finite distance. It differs from a mathematical dipole in that the latter source-sink pair has infinitesimal separation with a finite product of source-strength times separation. In practice a mathematical dipole can be approximated closely by employing current-electrode spacing and size that are small compared with other dimensions of the system.

† The zero-potential contour is independent of the resistivity of the homogeneous medium. Tap water was used for convenience.

‡ The potential distribution at 1000 cycles per second is negligibly different from that at lower frequencies. This frequency was selected as a practical compromise among adverse effects of electrode polarization, system-shielding and obtainable bridge balance. There is no measurable phase shift at this frequency.

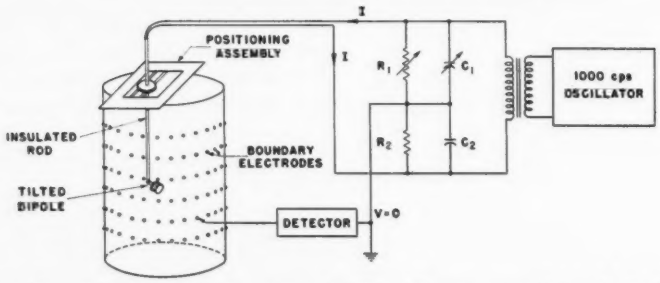


FIG. 3. Experimental arrangement for measuring the null contour on the wall of a homogeneous conducting cylinder. Boundary pickup electrodes are spaced 18 degrees apart radially and lie in planes 2.5 inches apart. The oscillator is a Hewlett-Packard Low-Frequency Oscillator, Model 202B; the detector is a Hewlett-Packard Amplifier, Model 450A in cascade with a Hewlett-Packard Harmonic Wave Analyzer, Model 300A; the bridge transformer is a General Radio, Type 578A. The entire system is shielded, including a screen cage for the cylinder. See text for discussion.

the desired zero reference potential, which is the electrical midpoint between the two current electrodes taking the discontinuity owing to polarization into account, by first optically aligning the finite dipole on the cylinder axis midway between the end caps. The detector is then connected to a boundary pickup electrode which lies on a circle whose plane passes through the geometric midpoint of the dipole. Then the bridge is balanced by adjusting $R_1$ and $C_1$ for a null reading on the detector. This procedure circumvents the pronounced adverse effects of electrode polarization.

With a dipole current of 0.4 milliampere at 1000 cycles per second, the applied voltage to the dipole is 0.05 volt and the bridge null remains less than 0.5 microvolt for short periods (20 to 30 minutes) and less than 5 microvolts for periods of four to five hours. These null voltages correspond to bridge balances of 100,000:1 (100 decibels) and 10,000:1 (80 decibels), respectively. The small departures from zero are attributable to thermal gradients in the medium, polarization-impedance fluctuations and irreducible effects of stray capacitance and stray pickup voltage. The maximum boundary voltage on the cylinder under the above conditions is 0.6 millivolt; thus, it can be seen that even long-period drifts of 5 microvolts represent an error in the reference potential of less than 1 per cent of the maximum boundary voltage.

With the reference potential established in this manner, the detector can then be connected to other pickup electrodes and the dipole position can also be changed. The detector voltage readings (which are unbalanced bridge voltages) represent voltages with respect to the dipole mid-potential since the potential established at the grounded point of the bridge remains as initially set regardless of shifts of dipole position or connections of the detector to various pickup electrodes. Therefore, the null contour on the cylinder boundary can be measured directly* for a variety of dipole positions and orientations.

## RESULTS

Using the method described, the null contours on the wall of the cylinder were determined for various known positions and orientations of the finite dipole for both centric and eccentric cases. The complete results have been published elsewhere.[14] A portion of the centric results will be given here.

For centric dipoles located midway between the endcaps of the cylinder and tilted with respect to the cylinder axis by angles ranging from 0 degrees to 45 degrees (or 135 degrees to 180 degrees) the null contour is approximately an ellipse (to an accuracy of a few per cent for tilt angles equal to 20 degrees or less) and is indicated by the shaded band in figure 4. In order to describe the null contour it is convenient to designate the $z$ coordinate of the null contour with respect to a plane perpendicular to the cylinder axis which passes through the dipole, defined by $z = 0$. The line joining the points where the null contour passes through $z = 0$ is perpendicular to the plane in which the dipole is tilted, while the maximum values of $z$, designated by $z_m$ in figure 4, occur symmetrically in the plane in which the dipole is tilted.

It can be shown[14] that the null contour is a

* Usually the null contour lies between pairs of pickup electrodes which are fixed in position, and must be computed by interpolation.

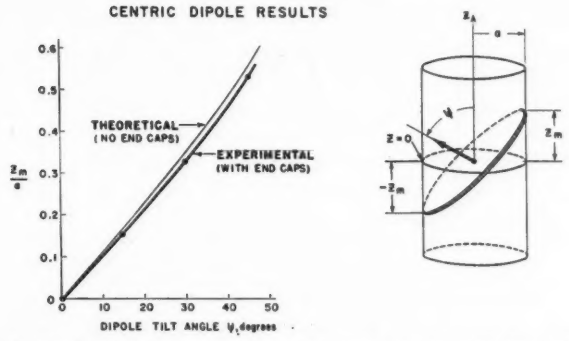


FIG. 4. A centric dipole tilted at an angle $\psi$ with respect to the cylinder axis is shown at the right with the approximately elliptical null contour it produces, indicated by the shaded band. The experimental results are shown at the left and compared with a theoretic curve which pertains to an infinitely long cylinder, and which lies slightly above the experimental curve as expected.

function of the *ratio* of $z$ to the cylinder radius $a$. Consequently, the ratio $z_m/a$ plotted in figure 4 as a function of dipole tilt angle is applicable to cylinders of any radius provided only that the ratio of cylinder length to diameter is about the same or greater than that employed experimentally; that is, about 2 or greater.

The experimental results given in figure 4 are compared with a theoretic curve* which pertains to an infinitely-long cylinder. The fact that the theoretic curve lies slightly above the experimental curve is to be expected since the effect of end caps on the cylinder is to shift the null contour closer to $z = 0$. The general behavior of the two curves is similar, however, and the closeness of the agreement between them indicates the soundness of the experimental results which are accurate to approximately 5 per cent.

With these experimental data it becomes possible to determine quantitatively the errors of the perpendicular-plane construction. For the case of a centric dipole, the erroneous tilt angle, $\psi'$, (see fig. 2) is related to the maximum coordinate of the null contour by the equation $z_m/a = \tan \psi'$, which enables $\psi'$ to be calculated if $z_m/a$ is known. The erroneous tilt angle is always less than the true tilt angle owing to the bending over of the zero-potential surface within the cylinder as illustrated in figure 2. For a numerical example, suppose $z_m/a$ is assigned the values $\pm 0.33$, which corresponds to a true tilt angle of 30 degrees as can be seen in figure 4. The erroneous tilt angle is then given by $\psi' = \tan^{-1} 0.33 = 18.3$ degrees, a discrepancy of about 12 degrees in this case. A plot of the erroneous tilt angle obtained by means of the perpendicular-plane construction versus the true tilt angle is given in figure 5. This curve was derived by the method of calculation illustrated in the above example. The curve is very nearly a straight line with an average slope of approximately 0.6, which means that the angle obtained from the perpendicular-plane construction is about 60 per cent of the actual tilt angle.

When the dipole is moved to an eccentric position, the simple and symmetric behavior exhibited by the centric dipole field is no longer observed. The discrepancy between the true angle of dipole tilt and the apparent angle, as measured by null contour technic, cannot be described by a simple constant correction factor as in the centric case, but assumes major complexities. With an eccentric dipole the null contour deviates markedly from an ellipse,

* The equation [14] of this curve is

$$\tan \psi = \frac{\pm \int_0^\infty \frac{\sin\left(k\frac{z_m}{a}\right) dk}{I_1(k)}}{\int_0^\infty \frac{k \cos\left(k\frac{z_m}{a}\right) dk}{kI_0(k) - I_1(k)}}$$

where $\psi$ is the tilt angle between the dipole axis and the cylinder axis, $I_0(k)$ and $I_1(k)$ are modified Bessel functions and $k$ is a variable of integration.

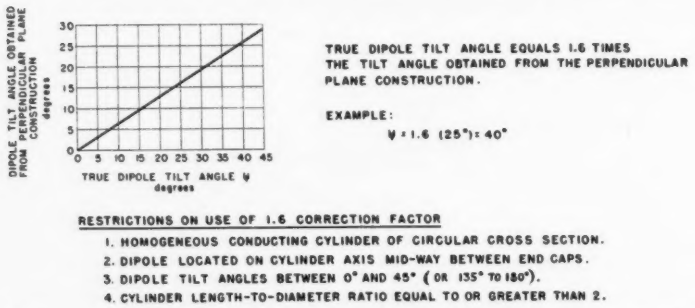


FIG. 5. The experimental results are compared with the perpendicular-plane results in the form of the curve in the upper left where a constant correction factor of 1.6 for dipole tilt angles ranging from 0 degrees to 45 degrees (or 135 degrees to 180 degrees) is seen to be applicable. The restrictions on the use of this correction factor are listed and should be recognized as limitations in applying this result in electrocardiography.

and the constructed plane which fits this contour most closely does not contain the dipole center. Furthermore, deviations between the true tilt angles and apparent angles obtained on the arbitrary assumption of a centric dipole, exceed the 60 per cent discrepancy applicable to the centric case. The influence of eccentricity is presented in detail elsewhere.[14]

## DISCUSSION

It will be noted that dipole tilt angles up to only 45 degrees were employed. This was done mainly because the cylinder end caps play an increasingly important role for larger tilt angles; indeed, a portion of the null contour appears on the end caps rather than lying entirely on the cylinder wall for tilt angles that are too much in excess of 45 degrees for the cylinder used experimentally. The results of a study of the end-cap effects would apply only for the specific cylinder used and would not be as general as those presented. Although the correction factor for tilt angles exceeding 45 degrees has not been explored, it is obvious that the factor 1.6 is not applicable for all tilt angles because when this angle is 90 degrees, for instance, the null contour and perpendicular plane can be seen to agree exactly from symmetry.

The theoretic complexities of the cylindric volume conductor are well illustrated by the null contour equation for an infinitely long cylinder which appears in integral form and involves nonelementary functions. The solution for a cylinder with end caps is even more complicated; so much so that it becomes rather impractical to utilize the solution conveniently. Furthermore, the null contour behavior when the dipole position is not on the axis of the cylinder lends a considerable amount of additional complication.[14]

The dipole angle error entailed in the perpendicular-plane construction depends, in part, on the shape of the homogeneous volume conductor in which the dipole is immersed. This study has been devoted to cylindric conductors because they have been advocated in the application of the null-contour technic. However, when the perpendicular-plane construction is applied to both centric and eccentric dipoles in a homogeneous spherical volume conductor, the errors of the construction are surprisingly small, as can be shown by unpublished theoretic analyses. For dipole eccentricities up to 20 per cent of the sphere radius, the maximum discrepancy between the true angle and the apparent angle obtained from the perpendicular-plane construction is only approximately 3 degrees, and is less than 6 degrees for dipole eccentricities as large as 40 per cent of the sphere radius. These errors are much less than those encountered in a cylindric conductor. The claim has been made that the cylindric representation of the human subject is superior to the spherical representation; however, from the standpoint of the perpendicular-plane construction itself, the

use of a spherical medium has the advantage of negligible constructional errors.

In these studies it is shown that the analysis of vectors solely by the null-contour technic in a cylindric system results in large errors inherent in the utilization of the perpendicular-plane construction itself. Even in the most simplified case, with centric position of the dipole at a tilt of not greater than 45 degrees from the vertical, the true angle of tilt is greater than the constructed angle by approximately 60 per cent. Since, within the restrictions listed in figure 5, the disparity between the true and apparent angles increases linearly with increasing tilt, it is possible in a simple manner to convert apparent angles to the true angles in the idealized schema. The application of a correction factor might be attempted in the human subject according to the following example. Suppose the total difference between the maximum $z$-coordinates of the null contour is $A$ inches, and the cylinder fitted to the human subject has a diameter of $B$ inches. The dipole tilt angle given by the perpendicular-plane construction is then $\psi' = \tan^{-1}(B/A)$. This angle may then be multiplied by 1.6 to obtain a corrected result. For instance, if $A = 5$ inches and $B = 12$ inches, then $\psi' = \tan^{-1}(5/12) = 22.6$ degrees, which is the angle computed from the perpendicular-plane construction. The actual dipole tilt angle is then given quite closely by 1.6 (22.6 degrees) $\doteq$ 36 degrees. The application of this factor of 1.6 to the human subject is necessarily a first approximation at best, and of very dubious value because of the obviously eccentric position of the human equivalent dipole, if for no other reason.

An alternative method for determining the mean vector spatial orientation is also used. Precordial leads are used to establish the point at which the null contour intersects with the transverse plane through the heart center. Limb-lead data provide the requisite additional information. Errors entailed in this method are quite different from those relying exclusively on the null contour. Therefore, the results of the two methods cannot be expected to be in agreement.

Whereas it is generally conceded that vector analysis of the electrical field of the heart by the null contour technic yields only approximate results, it is shown here that the errors resulting from misapplication of physical principles are of considerable magnitude. These errors are superimposed upon the limitations inherent in the many assumptions applied to field analysis of the electrical forces of the heart.

## Summary

1. The essential ideas underlying mean spatial vectors and null contours are reviewed briefly. The perpendicular-plane construction in a cylindric volume conductor, as employed in conjunction with null contour for the measurement of heart vectors, is clarified conceptually.

2. Experimental apparatus for the quantitative determination of true dipole angles in such a construction is described.

3. The discrepancy between true dipole angle and apparent angle obtained from the null-contour, perpendicular-plane construction for the most simplified case, a centric dipole position, is found to bear a ratio 1.6/1.0 with the restriction of a maximum 45 degree tilt of the dipole from the vertical.

4. The dependence of the dipole angle error on boundary shape is discussed.

5. Limitation of the application of a "correction factor," effective in the idealized cylindric schema, to the null-contour technic is emphasized.

6. Major limitation of the usefulness of the null-contour technic for analysis of spatial vectors on other than an empiric basis is implied.

## Acknowledgment

The authors express appreciation for the painstaking care of Mr. Chauncey Elliot in the design details and construction of the cylinder electrodes, finite dipole and dipole positioning assembly.

## Sumario Español

1. Las ideas esenciales sustentando los vectores espaciales promedioy los contornos tornados se repasan brevemente. La construcción de plano perpendicular en un volumen cilíndrico conductor, empleandose en conjunción a con-

tornos tornados para la determinación de vectores cardíacos, se clarifica conceptualmente.

2. Aparatos experimentales para la determinación cuantitativa de ángulos dipolos verdaderos en tal construcción se describe.

3. La discrepancia entre ángulos dipolos verdaderos y ángulos aparentes obtenidos de los contornos tornados de construcción de plano perpendicular en el caso mas sencillo, una posición dipolo céntrica, se encontró tener una razón de 1.6/1.0 con la restricción de una inclinación máxima de 45° del dipolo con la vertical.

4. La dependencia del error de ángulo dipolo en la configuración del lindero se discute.

5. La limitación de la aplicación de un "factor de corrección," efectivo en el esquema cilíndrico idealizado, al uso clínico de la técnica de contorno tornado se enfatiza para el estimado absoluto de dirección vectorial y para la comparación de los ángulos QRS-T.

6. Mayor limitación del uso de la técnica de contorno tornado en el analisis de vectores espaciales en otra que en una base empírica se implica.

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# A Simple Geometric Analysis of Cardiac Potentials as Recorded at Points Close to the Heart

*By* MANUEL GARDBERG, M.D.

A simple geometric method is employed to investigate the theoretically expected potentials at an electrode close to the heart as a dipole moves about in an area in the chest occupied by the heart. The considerable error resulting from the assumption that the dipole remains at the center of a geometric frame of reference is thus disclosed. It is pointed out that errors in polarity which occur cannot be compensated for by alteration of the characteristics of the recording device. It is suggested that such errors account for the finding by spatial vectorcardiographers that many normal QRS loops point forward, a finding which does not correlate well with the Gardberg-Ashman hypothesis of ventricular accession. It is further suggested that the limb leads are not free of these effects and that exaggeration of the electrical rotation of the heart is thus accounted for. It is further pointed out that derivation of precordial potentials from vector loops or vice versa is not permissible.

IN the measurement of cardiac potentials by means of electrodes placed on the surface of the body, it has generally been assumed that the body acts as a volume conductor of more or less homogeneous conductivity. With regard to the limb leads, it has long been assumed that the heart lies at the center of an equilateral triangle and that the potentials as recorded at the extremities may be regarded as originating from a point source (representative dipole) situated at the center of the triangle. The relative accuracy of the concept has usually been attributed to the relatively great distances between the shoulders and left leg on the one hand and the heart on the other, and to the assumed equidistance of these three points from the heart. Much useful work was based upon this assumption.

When methods were devised for recording spatial vectorcardiograms, some of the same assumptions were retained. The advocates of both the "tetrahedron" and the "cube" originally assumed that the heart might be regarded as being placed at the center of these geometric figures. Corrections were made for lack of equidistance of the electrodes from the heart and between electrodes so as to bring the advocated geometric figures into approximate theoretic accuracy.

Certain curious findings reported by spatial vectorcardiographers (for example, the loop pointing forward in so many normal persons) impelled the author to make the following analysis of the effect of placing electrodes in various relationships to a series of waves of excitation of the same size and orientation in space.

Figure 1 represents a series of waves of excitation moving in the line, AB, and approaching the point B. The waves are so oriented that their plane is perpendicular at AB and therefore the line, AB, in addition to being the direction of the motion, is also the direction of the electrical axis of the waves. If an electrode is placed at B and the entire system is immersed in an homogeneous conducting medium, the potentials at B may be regarded as being proportional to the solid angle subtended at B by the margins of the waves of excitation. In calculating the theoretically expected potentials at the points B and A, we may, under these circumstances, employ the simplified formula, $VE \cos \theta/d^2$, where $E$ is the electrical moment of the waves of excitation, $\theta$ is the angle between its electrical axis and the line joining the center of the wave of

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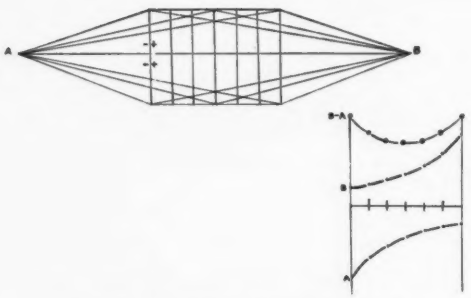

FIG. 1. A series of waves of excitation approaching the electrode B. The curves record the potentials at the electrodes B and A respectively and (B–A) the difference of potential recorded on the bipolar lead.

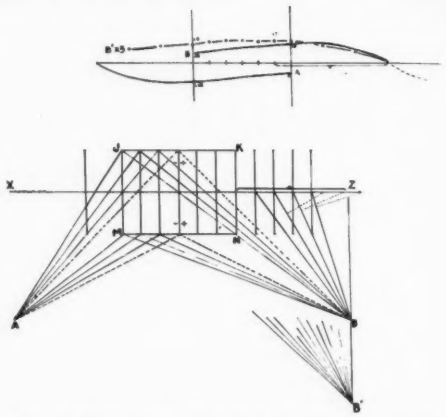

FIG. 2. The curves B and A result from plotting the potentials at electrodes B and A as the wave of excitation moves from X to Z. The curve B′ × 3 results from plotting the potentials calculated for B′ (multiplied by 3) as the wave of excitation moves from X to Z. The dashed extension of curve B represents the potentials which would be recorded at B if the waves of excitation should proceed past the point Z. In the upper part of the figure the portions of the curves between the two vertical lines correspond to the waves of excitation in the closed figure, JKMN.

excitation to the electrode, and $d$ is the distance between the center of the wave of excitation and the electrode.

In figure 1, $\theta = 0$, and since $\cos 0° = 1$, we may eliminate this factor from the formula. A 40 mm. vector was assigned to represent the electrical moment of each wave of excitation and the value, $40 \times 1/d^2$ was plotted as the theoretic potential of each of the electrodes A and B. This was repeated for every position of the wave of excitation and then the difference of potential, B minus A, was plotted (curve B–A, fig. 1) for the bipolar lead BA. It is readily seen that the potential at B increases more and more rapidly as the wave of excitation approaches B. An electrode, A, at equal distance from the closed figure would record a negative potential whose curve would simply be the reverse of that recorded for B. The top curve of the figure represents the difference of potential between B and A at the same time. Obviously, from the curves for the situation as represented in figure 1 identical electrical moments of the successive waves of excitation are not accurately reflected in the potential of the single electrode as they must be if the wave of excitation is to be regarded as always being situated at the center of the figure. The bipolar lead does much better, but there is a sag in the curve of considerable proportions. If the electrodes are placed at greater and greater distances from the closed figure the magnitude of the potentials will diminish, but the sag in the bipolar curve will begin to straighten out, and the sharp ascent of the hyperbola of the unipolar curve will be eliminated. At infinity both curves will be perfectly flat. It is doubtful that sufficient distance can be achieved within the confines of the human body to flatten even the bipolar curve to a great extent.

Figure 2 represents the effect of a similar set of waves of excitation upon two electrodes, A and B (separately and as a bipolar lead), which are on a line parallel to the axis, XZ, of the waves of excitation but at some distance, BZ, from the axis XZ. One might regard the electrodes as having been moved along two opposite sides of the body to the new positions. Here one sees that the potentials recorded at the electrodes, though smaller in magnitude than those recorded by the electrodes of figure 1, tend to vary in magnitude much less for the unipolar as well as the bipolar lead for those waves of excitation in the range of the closed figure, JKMN, and close by. However, as the wave of excitation approaches Z, one can see both from the solid angle and inspection of the curve B, that there is a more or less critical area closer to Z in which movement of the

wave of excitation toward Z causes a rise and then a rapid fall in potential. Thus, if the closed figure, JKMN, is moved to the position indicated by the bracket (fig. 2), the potentials recorded by the waves would vary tremendously; great inaccuracy would be introduced. Thus, for the situation represented by figure 2 we see that there is a middle area in which a bipolar lead, B minus A, (see curves, fig. 2) is accurate within limits *which could not be achieved by distance alone within the confines of the human body for the situation represented in figure 1.* This flatness of the curve results from the fact that the two factors, cos $\theta$ and $1/d^2$, tend to compensate for one another within this area and because the variation in the potentials of the two electrodes compensate for one another. For this middle area the potentials behave as if the wave of excitation is always at the center of the figure. The existence of the critical area enclosed by the brackets should be remembered as it will be referred to later. *No alteration of the characteristics of the recording apparatus can correct for the errors occurring in this critical area.*

Let us now consider the effect of moving the electrode B to a new position B′ (fig. 2) so that the electrode lies on an extension on the line, BZ, and so that the distance BZ increases to B′Z. Under these circumstances the theoretically calculated potentials become much smaller so that each was multiplied by three before being plotted in the form of the curve B′ × 3 (fig. 2). The potentials at B′ are seen to be more constant and therefore more "accurate" in the middle area, but there is a greater drop in the area enclosed in the brackets. When the curves for the potentials at B and B′ are compared (upper part of fig. 2) it is noted that both curves reach zero at the same time.

Attention is directed to the fact that a unipolar electrode oriented as in figure 1 records a rapid increase in its potentials as the wave of excitation approaches it in the critical area, while the same electrode moved over as in figure 2 records a rapid drop of its potentials as the wave of excitation approaches it.

Figure 3 portrays a series of waves of excitation oriented perpendicular to those treated

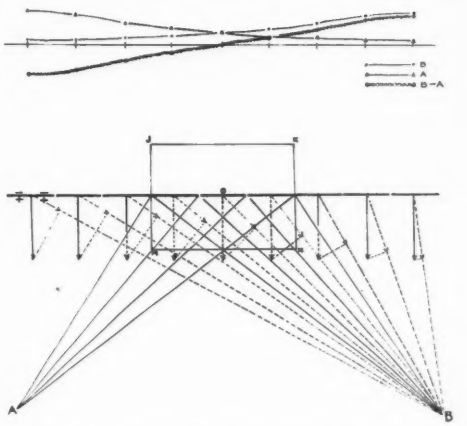


FIG. 3. A series of small waves of excitation oriented perpendicular to the direction of those of figures 1 and 2. The electrical moment of each of the waves is represented by a vector of the same magnitude and direction and is treated as in figures 1 and 2. Since both electrodes are "facing" the same surface of the waves they will both have the same sign, but the difference of potential B minus A becomes negative when the potential at B is less than that at A.

in figures 1 and 2. It is obvious that beginning at the left side of the figure the positive solid angle subtended at B begins rather small and becomes progressively larger as the wave of excitation is placed closer to the electrode. The solid angle subtended at A is also positive and behaves in the reverse manner. A considerable error is present in the unipolar leads and is even greater in the bipolar lead. Within the closed figure the wave of excitation, 0, at the center will register a zero potential for B–A. However, the wave of excitation to the left of 0 gives a negative potential on the bipolar lead B–A and the wave of excitation to the right of it gives a positive potential on this lead. If such a lead is employed to determine the anterior-posterior projection of a "horizontal" vectorcardiogram this error will occur. The vector will have the proper direction if the wave of excitation is at the center of the figure, but a similarly oriented wave of excitation nearer the surface of the body will cause the vector to appear to be directed forward while if it happens to be back of the center it will be made to point backward. *No constant*

*alteration of the characteristic of the apparatus can correct for this error.*

Consider in figure 3 the movement of a series of waves of excitation in a vertical direction, from JK to MN. Insofar as the unipolar electrodes are concerned, the potential would behave as in figure 2 (see curve). The difference in potential of a bipolar lead, B minus A, would behave as represented in the curve in figure 3 except that as the wave of excitation approaches the line, MN, the potential at the end of the curve first becomes greater, then, where the critical area described in the discussion of figure 2 is reached the potentials all drop off very rapidly. The potential for any single wave of excitation will retain its error for the bipolar leads. The magnitude of the potential will first increase and then drop off rapidly.

In the next step of this analysis (fig. 4), the close electrode B and the more distant electrode B′ (of fig. 2) are kept on the same line, B′Z, but the axis of the waves of excitation and the line upon which they move, XZ, are tilted through an angle of approximately 30 degrees. The waves of excitation are supposed to move successively from *a* to *b* to *c*, etc. It is to be remembered that the positive charges are on the advancing surface of the wave of excitation.

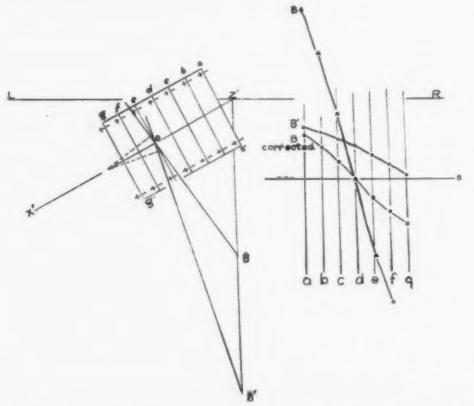


FIG. 4. This figure represents the effect upon the potential at a close point, B, and at a greater distance, B′, when the axis of the waves of excitation, X′Z′, is at an angle to the line, BZ′, upon which the electrodes lie. The right hand side of the figure shows the curves for the potential B and B′ and for B corrected for distance. For complete discussion see text.

We can assume that the closed figure, *a*, *a′*, *g*, *g′*, containing the waves of excitation *a*, *b*, *c*, *d*, *e*, *f* and *g*, represent the heart. It is placed, in accord with the anatomic facts, largely to the left of Z, the geometric center of the Einthoven triangle in the frontal plane. The line, LR, is the line of lead I. B may be regarded as the back electrode of the tetrahedron and is placed one-half as far from Z as is B′. B′ is a hypothetic back electrode placed at the mathematically correct position for the tetrahedron. Calculation of the theoretic potentials produced by the waves of excitation *a*, *b*, *c*, *d*, *e*, *f* and *g* at B and B′, after correction of the potentials at B for the difference in the distance should throw some light upon the validity of the practice of correcting for distance by constant alterations of the amplification employed in recording.

On the right hand side of figure 4 are the curves plotted for the potentials produced at B and $-B'$, together with the curve for the potentials at B after "correction" is introduced. Since B is one-half the distance it should be from Z its potentials must be divided by 4 (the inverse of the square of the distance). Examination of the curves show that from *a* to *d* the "corrected" potentials at B show discrepancies in magnitude as compared to the potentials at B′ which, we may recall, was placed at the mathematically correct position for the tetrahedron. *From* d *to* g *the potentials recorded at B show a discrepancy in polarity* with respect to B′. Obviously, no constant alteration of the characteristics of the apparatus can compensate for these phenomena. The construction lines were left on the figure for the wave of excitation, *e*, to show more clearly how the error in polarity is produced. It is believed by the writer that positions *a* to *g* represent possible orientations of waves of excitation in various human hearts, relative to the electrode B. Thus, it is seen in figure 4 that the curves for the potentials $V_B$ and $V'_B$ are similar to those of figure 2 but that they are now out of phase.

The graphic application of this type of analysis to the problems of the human electrocardiogram is impossible without some concept of the path of accession during the inscription

of the QRS complex. The only detailed concept available is that which was published by Gardberg and Ashman in 1943. In figures 5, 6, 7, 8, and 9, five of the successive stages in the process of excitation of the ventricles are represented. The hearts are represented as being viewed from above so that the loop described by the tips of the vectors representing the electrical moment of the successive stages is the hypothetically correct horizontal loop. Two hearts are represented in each figure; one, *b*, is in such a position that its apex is placed a bit backward from the average position, and the other, *f*, is in such a position that the apex is directed more forward. B and B′ are two electrodes placed on a line which is perpendicular to the frontal plane at the center of the Einthoven triangle. B′ is a hypothetic electrode which is placed at the mathematically correct distance for the back electrode of the tetrahedron. B is supposed to be the back electrode actually employed in the tetrahedron and is one-half as far from the frontal plane as is B′.

The vector for each stage in each figure is treated as in figure 4 for the two back electrodes and the theoretically expected potential at B and B′ are thus calculated. In addition, each vector is also projected upon the line of lead I, and the theoretic potential on lead I is calculated. Finally, for each vector, the potential of each back electrode is plotted against the potential reflected on lead I, and the resulting loops were recorded in the upper part of each figure in the same manner as these potentials would be recorded as the horizontal loop by the cathode ray oscilloscope. Since identical lead I potentials are employed in plotting both the B and B′ loops, the differences between the two loops are entirely the result of the differences in the back potentials. The points on the loop plotted for B are marked as deltas; the points on the loop for B′ are marked as circles. The construction of the potentials on lead I is omitted in figures 7, 8 and 9 as it would cause confusion.

At 0.015 second, figure 5, the loops diverge widely, largely because of the difference in the distance, for the projections upon the lines of the lead are almost equal. Such an error is

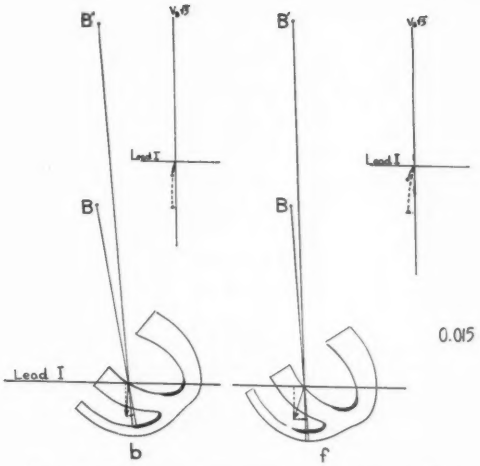


FIG. 5. The heart is represented in two positions, (b), apex back, and (f), apex forward. In this and the succeeding figures the waves of excitation in the two sides of the septum are omitted since they virtually neutralize one another and would only complicate the diagrams. The same lead I (see text) is employed in constructing the solid line loop produced by B and the dotted line loop produced by B′.

The heavy black lines on the diagrams of the heart of figures 5, 6, 7, 8, and 9 represent the waves of excitation at the times indicated.

correctible by introducing a correction factor in amplification. However, at 0.025 second, in the case of the heart *b*, of figure 7, there is actually an error in polarity as indicated by the fact that the vector is made to appear to point forward by the potential at B, whereas it actually points backward as plotted for the potential at B′. Correction by amplification adjustments for distance cannot change the polarity. At 0.04 second, in the case of heart, *f*, of figure 8 the vector is again made to appear to point more forward by B than by B′. The customary reduction of amplification as a correction for distance would make the error worse. If the apex were a bit more forward so that the vector occupied the position, F, the record made with B would cause the point on the loop at 0.04 second to appear at delta F (upper part of figure 8, *f*).

The summary of the effect of "correcting" the potentials at B for distance is shown on figure 9. The finely dotted loop is that obtained by "correcting" the potential of B for distance.

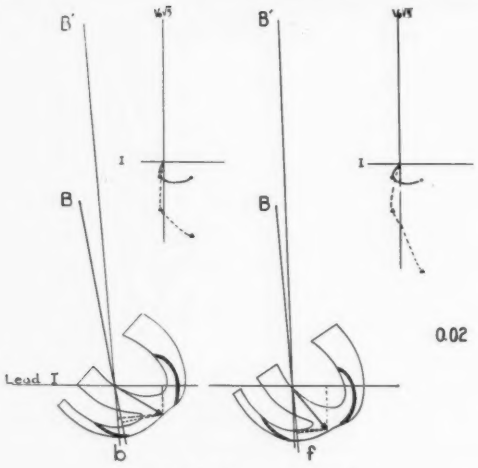


FIG. 6. See legend, figure 5.

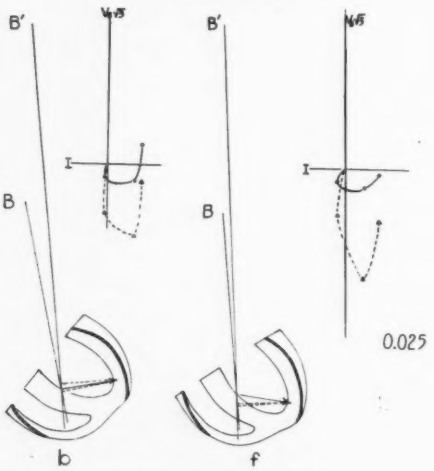


FIG. 7. See legend, figure 5.

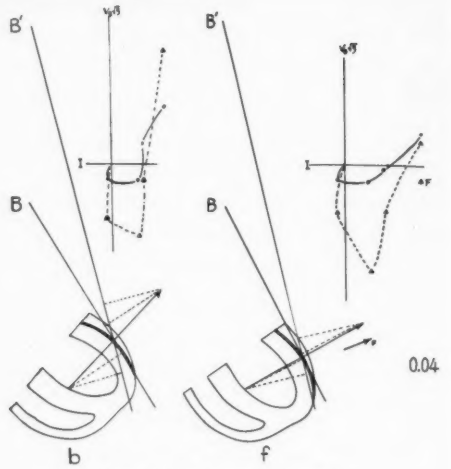


FIG. 8. See legend, figure 5.

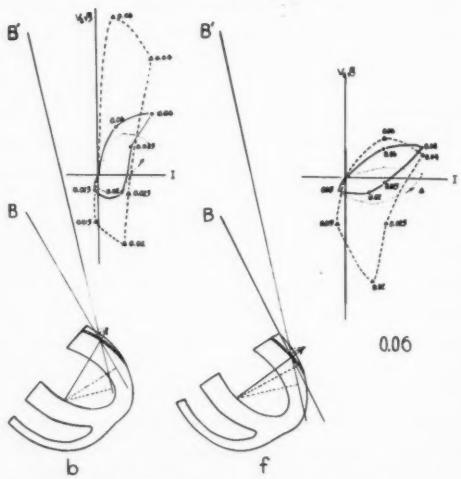


FIG. 9. The finally dotted loop is loop B "corrected" for distance. The completed loops show the two "types" of loops produced by use of a close back electrode even though the actual loop is the same but differently oriented in space. The more distant (hypothetical) electrode B makes much less error. However no constant correction for the closeness of B would compensate for the errors occurring in the loops made with the close electrode.

This is accomplished by dividing the potentials at each point on the loop for B by 4 (for B is one-half the distance from the frontal plane as is B′). A comparison of the "corrected" loops of the upper part of the figure 9, with the corect loops plotted by employing the potentials at B′ shows that for some vectors the correction is adequate (*b*, 0.015 second); for others there is a discrepancy in magnitude of the potential and for still others there is a discrepancy in polarity. The resulting errors in the direction of the various instantaneous vectors are obvious from the figures.

Incidentally, it is noted that although they are derived from the same actual loop (though differently oriented in space) the two "corrected" loops (finely dotted loops of figure 9) correspond to the two types of loops which Burch[1] found among normal hearts. One, *b*, figure 9, is more rounded and has a more backward mean direction, the other, *f*, figure 9, has

a mean direction which is parallel to the frontal plane or is directed a bit forward. In this analysis it is seen that this phenomenon results from only a moderate change in the position of the heart. If figures 4 and 9 are reviewed carefully it is seen that the eccentricity errors of the electrode B have a tendency to "spread" the direction of the vectors to forward positions over a rather wide range. This automatically tends to divide a naturally even distribution of vector directions into two main groups.

It must be remembered that in actual recording, the potential $V_B$ is measured against the central terminal. Throughout this analysis it has been assumed that the central terminal remains at zero potential. A further analysis leads to the conclusion that this assumption must be discarded. It was found that the variations of the central terminal potential is such that the error described will be modified for transverse and counterclockwise hearts. However, when the axis of a wave of excitation is at more than plus 30 degrees and it is eccentric in the same direction, as one might consider normal for the lateral wall of the left ventricle, the central terminal is less negative in relation to the back potential and the vector is made to appear to point forward when it actually has a backward direction of 30 degrees behind the frontal plane. A detailed analysis will be presented in a subsequent paper. It is important to note that this finding correlates well with the fact that one notes that, of the two groups of loops reported by Burch, those which point forward are generally loops which have a mean axis of more than +30 degrees on the frontal plane, while those which point backward have a more transverse axis on the frontal plane. The corresponding error of the cube is not nearly as great as that of the tetrahedron.

Throughout this analysis it has been assumed that one may represent each wave of excitation by a single dipole situated at the center of the wave. An error is involved in this assumption. This error does not significantly affect the inferences drawn in this discussion.

## Summary and Conclusions

A theoretic analysis of the potentials recorded at electrodes relatively close to the heart is accomplished by employing a simple geometric approach.

The error resulting from the assumption that a wave of excitation undergoing linear motion remains at the geometric center of certain frames of reference is analyzed.

The assumption that alterations in amplification may be introduced to correct for electrode distance is examined.

It is concluded that errors resulting from the assumption that the wave of excitation remains at the geometric center of any frame of reference are of greater proportions than has been recognized in the past.

It is further concluded that it is impossible to correct for closeness of the electrode by alteration in the amplification employed in recording.

The probable explanation of the recording of loops which point forward by both cube and tetrahedron technics is offered.

As a result of this analysis it seems apparent that attempts to calculate the precordial potentials from any spatial loop will be successful in proportion to the extent to which the vectorcardiogram contains errors in the same direction as those intrinsic in the precordial potentials.

It is suggested that the standard limb leads may suffer less from the errors described here than do chest leads, not only because of their distance but because they are bipolar leads.

It is further suggested that these eccentricity errors account for the exaggeration of the electrical rotation of the heart.

## Addendum

Since the preparation of this paper was completed two papers by Ernest Frank[2,3] have appeared which deal with the same problems in a more general mathematical manner. These classic papers are recommended highly to all those interested in electrocardiography. The approach which Frank employs is somewhat different from that employed by the author of the present paper. Both approaches seem valid. The approach employed in the present paper is a more simple geometric one and may serve to aid in visualization of the principles involved in considering the effect

of eccentricity of the dipole and the necessity for discontinuing the practice of ignoring it.

### Acknowledgment

I wish to acknowledge the help of Dr. Richard Ashman, for whose suggestions and encouragement I am deeply grateful.

### Sumario Español

Un analisis teórico de los potenciales registrados en electrodos relativamente cercanos al corazón se logra empleando un sencillo aproche geométrico. El error que resulta en la suposición de que una onda de excitación propagandose en línea recta permanece en el centro geométrico de ciertos marcos de referencia se analiza. La suposición de que alteraciones en amplificación pueden ser introducidas al corregir la distancia de electrodo se examina. Se concluye que los errores que resultan de la suposición de que una onda de excitación permanece en el centro geométrico de cualquier marco de referencia son de mayores proporciones de lo que se había creido en el pasado. Además tambien se concluye que es imposible corregir para cercanía de electrodo mediante alteración en la amplificación empleada durante el registro del trazado. La explicación probable del registro de ondas que apuntan hacia adelante usando ambas técnicas de cubo y tetraedro se ofrece. Como resultado de este analisis aparece aparente que los atentados a calcular los potenciales precordiales de una onda espacial tendrán buen resultado en proporción a la extensión a que el vectorcardiograma contenga errores en la misma dirección como aquellos intrínsecos en los potenciales precordiales. Se sugiere que las derivaciones clásicas de las extremidades puedan sufrir menos de errores descritos aquí que las derivaciones del pecho, no tan solo por la distancia pero debido a que son derivaciones bipolares. Además se sugiere que estos errores de excentricidad explican la exageración de la rotación eléctrica del corazón.

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# Whole Blood Volume Determined by Radiochromium-Tagged Red Cells

## Comparative Studies on Normal and Congestive Heart Failure Patients

*By* WILLIAM A. REILLY, M.D., RICHARD M. FRENCH, M.D., FRANCIS Y. K. LAU, M.D., KENNETH G. SCOTT, PH.D., AND WILLIAM E. WHITE, A.B.

Whole blood volume can be measured quite accurately by the use of radiochromium. The amount of radiation is very low; the radiochromium stays fixed in red blood cells for many hours and does not leave the circulation as may happen when plasma tags are employed. Hypervolemia was found in the majority of patients with right ventricular failure but not in those with left ventricular failure or mitral stenosis alone.

IN CONGESTIVE heart failure the blood volume has generally been considered to be elevated.[1, 6, 14, 15, 16, 18, 21, 24] Recent investigations by Prentice and co-workers[19] and by Ross and associates,[20] using $P^{32}$-tagged erythrocytes, have suggested that the blood volume in heart failure often is not increased. The importance of hypervolemia in both the physiology and therapy of cardiac failure has stimulated the study of this problem.

Nylin and Hedlund[16] in 1947 summarized the opinions of various investigators concerning the efficiency of the various methods. It was concluded that both the dye and the carbon monoxide methods may produce falsely high values because of leakage of dye substance from the vascular system and because of absorption of carbon monoxide by the myoglobin. More accurate determinations of blood volumes utilizing radioactive material[2, 4, 7-13, 15, 19, 22, 23] are now available.

Total blood volumes are usually calculated from either the red cell or plasma volume, utilizing the hematocrit reading. Higher values are usually obtained when calculating whole blood volumes from plasma volumes, presumably, because of leakage of plasma bound substances from the vascular space during the period between injection and sampling. Ross[20] has submitted some evidence to support Peter's contention that this loss may be accentuated in congestive heart failure. Plasma volumes determined by radioactive iodinated serum albumin do not differ significantly from those obtained from T-1824.[22] Since there are valid objections to the use of tagged-protein methods, we decided to use one of the radioactively labeled red cell methods.

Red cell volumes determined by tagging the erythrocytes with radiophosphorus,[11, 15] radioiron,[7, 8] and radiochromium ($Cr^{51}$)[9, 23] are approximately the same. Although all of the reported red cell methods employing radioisotopes may give consistent results, radiochromium seems to be the most useful for several reasons, which include the physical properties of $Cr^{51}$ and ease of application from a clinical viewpoint.

Radiochromium emits mainly a gamma radiation and a scintillation crystal detects this very efficiently. This permits a low injection dose and small blood samples. Radiochromium is rapidly taken up by the red cell in vitro. The tag stability is relatively constant for at least 24 hours in vivo as has been observed by Sterling and Grey[9, 10, 23] and by us.

Radiophosphorus on the other hand is a pure beta emitter, the counting of which, using a Geiger-Muller counter, involves corrections for mass absorption and coincidence. This isotope has less tag stability, necessitating sam-

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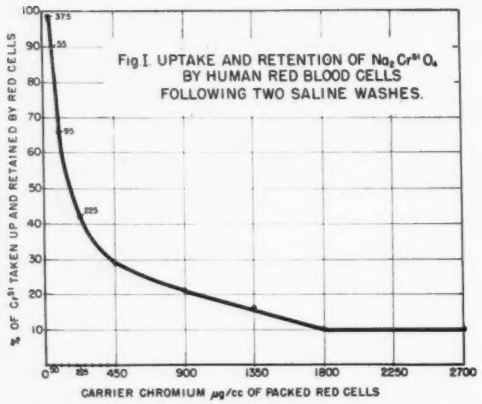


FIG. 1. Photograph showing uptake and retention of $Na_2Cr^{51}O_4$ by human red blood cells following two saline washes.

pling within 60 minutes or less following injection,[16] and its radiation effect because of beta emission is much greater than chromium.[51]

Nylin and Hedlund[16] have observed that mixing times in congestive heart failure are usually slower than in the normal individual and that an occasional patient may not show complete mixing until 30 or more minutes have elapsed after the initial injection. If samples are obtained before 30 minutes the sample counts may then be high, giving a false low volume. In this respect radioactive chromium has a definite advantage over radioactive phosphorus in the study of congestive heart failure since the stability of the former remains relatively constant for 12 hours or longer in vivo.

Radioiron was not considered because it is difficult to obtain and also requires the use of donor red cells tagged a week or more before injection.

## METHOD

Approximately 10 cc. of whole blood were drawn from the antecubital vein with a sterile heparinized syringe and transferred to a 15 cc. sterile rubber-capped pyrex tube into which was introduced 0.1 to 0.2 cc. of sodium chromate ($Na_2Cr^{51}O_4$) solution,* containing $Cr^{51}$ plus the inert carrier which had been processed into a neutral solution of $Na_2Cr^{51}O_4$. The $Cr^{51}$ activity of this solution ranged between 10 and 15 microcuries (μc) and the quantity of carrier chromium varied between 100 and 300 micrograms (μg.).

This blood sample containing the $Cr^{51}$ was agitated on a Fisher blood pipette shaker for 45 minutes at room temperature. Between 60 and 98 per cent of the $Cr^{51}$ (in $Na_2Cr^{51}O_4$) was taken up by the red cells, the variation being due to the total amount of chromium present in the solutions (fig. 1). The uptake of $Cr^{51}$ by red cells is inversely proportional to the amount of carrier $Cr^{51}$ present and our results agree with those published previously by Sterling and Gray.[9, 10, 23] It was also observed that lowered cellular uptake* of $Cr^{51}$ may take place when the cells are incubated in the presence of plasma; however, this difference was small enough to neglect for all practical purposes.

Following incubation and shaking, the tagged whole blood was centrifuged for five minutes at 2700 revolutions per minute (1559 gravities) and the plasma discarded along with the sodium chromate not taken up by the red cells. The tagged cells were washed three times with 5 or 6 cc. of sterile isotonic saline by means of inversion, the saline being separated by moderate centrifugation (five minutes at 1559 gravities) and discarded. This procedure removed any sodium chromate adherent to the red cells.

The last saline wash was found to contain less than 0.2 per cent of the $Cr^{51}$ present with the tagged cells. The cells were suspended in 5 or 6 cc. of saline by shaking them for a few minutes. Five tenths cc. of the cell-saline mixture was diluted to 50 cc. and 5 cc. portions of this were taken as a standard to determine the total number of counts present per cubic centimeter of the cell-saline mixture. The volume of the cell-saline mixture was carefully measured and administered to the patient by the intravenous route.

The dose to the patient was calculated to be the number of counts per second per cubic centimeter of cell-saline mixture times the number of cubic centimeters administered. In most cases the dose ranged from 4,000 to 20,000 counts per second.

In our hands 30 minutes was required for uniform mixing of tagged cells with those in the circulatory system of patients.† Samples of 6 to 7 cc. of venous

* The $Cr^{51}$ used in these studies was procured from either the Oak Ridge National Laboratory or Abbott Laboratories.

* It is felt that the presence of hemoglobin in the plasma may be responsible.[9]

† The results of mixing-time studies in normal individuals, employing serial samples taken 5, 10, 15, 20 and 30 minutes following the injection of tagged cells, indicated that complete mixing within the normal circulation may take place by 10 minutes, but it was not complete in all cases until 30 minutes. Therefore, in order to eliminate routine serial samples, a single 30 minute sample was selected for determination of the total blood volume. A wait of 60 minutes for complete mixing was selected for some cases of cardiac decompensation.

blood were taken with a heparinized syringe at time intervals of 30 minutes to 1 hour after the tagged cells were administered. The blood volume of the solution was estimated in cubic centimeters by computing the diluton of the tagged dose using the following formula:

$$\textit{Patient's blood vol. in cc.} = \frac{\textit{Total counts/sec./cc. injected}}{\textit{Counts/sec./cc. blood withdrawn}}$$

There has been considerable controversy over the validity of whole blood volumes calculated from hematocrit readings because of differences in large vessel and total body hematocrit. This debatable point was eliminated by the comparison of radioactivity in whole blood samples rather than red cell mass; the hematocrit was then used to determine red cell and plasma volumes. Ross and associates used a similar method with radioactive phosphorus tagged red cells.[20]

In the $Cr^{51}$ assay a 5 cc. aliquot of the standard was compared with a 5 cc. sample of blood withdrawn from the patient. All samples were pipetted into tin plate dishes which are 4 cm. in diameter. These were counted in a scintillation counter which was filtered so that only the 0.3 million electron volt gamma rays associated with the $Cr^{51}$ decay was observed as counts. The efficiency of the thallium-activated sodium iodide crystal was such that 11 to 14 per cent of the total disintegrations associated with gamma emission were observed as counts. On the average each sample of blood withdrawn from the patient after the tag was administered contained sufficient $Cr^{51}$ to have 4 to 20 counts per second per 5 cc. The samples were counted for a sufficient period of time to observe 4096 counts, which count has a statistical variation of less than 2 per cent. The scintillation counter was shielded with two inches of lead; this resulted in a background of 1.5 to 1.7 counts per second.

Numerous difficulties were encountered during the development of the procedure. Foremost was the poor quality of the radioactive chromium; the earlier samples contained low specific radioactivity and the blood volume results were unreliable. It is conceivable that on rare occasions, part of the tagged cells may have not been placed in the vein properly, with consequent leakage into the subcutaneous tissues giving falsely high blood volumes. Constant cross checking of the procedure and calculations by several individuals eliminated the human error to a great extent.

*Reliability of Method.* The reliability of this method was observed by comparing the results of two blood volume determinations on each of 17 subjects carried out within a two hour period according to the following double injection procedure.

Approximately 20 cc. of heparinized whole blood was withdrawn sterilely and divided equally between two pyrex tubes, one containing approximately 10,000 counts per second and the other approximately 20,000 counts per second and the samples processed for injection as previously described. One hour following the first injection of 10,000 counts per second a sample was withdrawn for assay and blood volume determined, and the counts per second per cubic centimeter recorded.

A second injection of 20,000 counts per second was then administered and another sample withdrawn after one hour and assayed. The activity due to the first injection was subtracted from the activity of the combined injection in order to determine the activity due to the second injection and the second blood volume determination.

Example:

$$\text{1st injection } \frac{10{,}000 \text{ c/s injected}}{2 \text{ c/s/cc. withdrawn}} = 5000 \text{ cc.}$$

$$\text{2nd injection } \frac{20{,}000 \text{ c/s injected}}{\underset{\text{Activity due to combined injection}}{6 \text{ c/s/cc.}} - \underset{\text{Activity due to 1st injection}}{2 \text{ c/s/cc.}} = \underset{\text{Activity due to 2nd injection}}{4 \text{ c/s/cc.}}}$$

$$= 5000 \text{ cc.}$$

The results of this experiment are shown in table 1. The difference in the two blood volume determina-

TABLE 1.—*Comparable Blood Volume by Repeat Determinations*

| *Patient | Blood Volume cc. | | Diff. cc. | % Diff. |
|---|---|---|---|---|
| | 1st inj. | 2nd inj. | | |
| 1 | 4170 | 4140 | − 30 | 0.7 |
| 2 | 4780 | 4600 | −180 | 3.9 |
| 3 | 3710 | 3890 | +180 | 4.6 |
| 4 | 4070 | 4030 | − 40 | 1.0 |
| 5 | 3830 | 4190 | +360 | 8.6 |
| 6 | 4330 | 4620 | +290 | 6.3 |
| 7 | 4150 | 4430 | +280 | 6.3 |
| 8 | 4390 | 4510 | +120 | 2.7 |
| 9 | 4460 | 4400 | − 60 | 1.3 |
| 10 | 3880 | 3940 | + 60 | 1.5 |
| 11 | 3010 | 3200 | +190 | 5.9 |
| 12 | 3280 | 3590 | +310 | 8.6 |
| 13 | 4300 | 4230 | − 70 | 1.7 |
| 14 | 4900 | 5440 | +540 | 10.0 |
| 15 | 4400 | 4380 | − 20 | 0.4 |
| 16 | 4730 | 4830 | +100 | 2.1 |
| 17 | 4280 | 4240 | − 40 | 0.9 |
| | | | Mean 169 cc. Range 30 cc. to 540 cc. or 0.4–10% | |

* All patients were recumbent at the time of these determinations.

TABLE 2.

| | cc. | cc./Kg. | L./M.² |
|---|---|---|---|
| Range..... | 2500–6084 | 45.8–81.0 | 1.79–3.05 |
| Mean ± Standard Deviation. | — | 65.5±5.95 | 2.49±0.28 |

tions in the same patient range from 30 to 500 cc. (0.4 to 10.0 per cent) with an average of 169 cc.

*Clinical Tests*

To establish normal values for our method we determined whole blood volumes on 89 male hospital patients whose illnesses presumably had little effect upon their usual blood volumes. Most of these patients were waiting for surgical repairs for hernia, hemorrhoids, or varicose veins. Patients with anemias, cardiac cachexia, dehydration, liver, kidney and heart disease were excluded from this group.

Blood volumes were determined in 56 patients with cardiac disease. These cases were divided into five groups on the basis of history, physical and clinical studies. Circulation times and venous pressures are not reported since they were not routinely determined at the same time as the blood volumes.

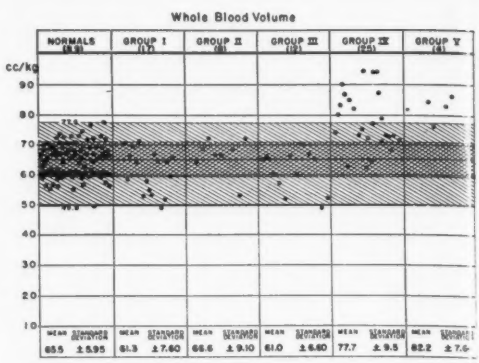


FIG. 2. Photograph showing whole blood volume in normal patients and in various types of cardiac patients in groups I to V.

*Group I* (17). Patients in this group had never had symptoms or signs of congestive heart failure but had various cardiac diseases such as hypertensive cardiovascular disease (HCVD), arteriosclerotic

TABLE 3.—*Patients in Group I Had Never Had Symptoms or Signs of Congestive Heart Failure, but Had Various Cardiac Diseases Such as Hypertensive Cardiovascular Disease (HCVD), Arteriosclerotic Cardiovascular Disease (ASCVD), Rheumatic Heart Disease (RHD), and Congenital Heart Disease (CHD)*

| Group I Pt., Age | Diagnosis | Ht., cm. | Wt., Kg., dry | Surface area, sq.M., dry | Total Blood Vol., cc. | Blood Vol., cc./Kg., dry | Total Blood Vol., L./sq.M., dry | PCV |
|---|---|---|---|---|---|---|---|---|
| B.C., 58 | ASCVD, old myocard. infarct | 183 | 72.7 | 1.94 | 5140 | 70.6 | 2.65 | 50.0 |
| C.J., 60 | ASCVD, angina | 176 | 67.2 | 1.72 | 3920 | 58.3 | 2.28 | 44.0 |
| C.M., 42 | HCVD | 172 | 61.0 | 1.70 | 4030 | 66.1 | 2.37 | 37.0 |
| C.O., 49 | HASCVD | 170 | 57.1 | 1.68 | 4040 | 69.4 | 2.41 | 35.0 |
| D.G., 53 | ASCVD, old myocard. infarct | 180 | 68.2 | 1.86 | 4380 | 64.3 | 2.36 | 43.0 |
| D.A., 53 | Malig. hypertens. | 173 | 66.3 | 1.80 | 4730 | 71.5 | 2.63 | 42.0 |
| F.F., 60 | HASCVD, old myocard. infarct | 177 | 74.0 | 1.90 | 3920 | 53.0 | 2.06 | 45.0 |
| F.E., 60 | HCVD | 164 | 55.2 | 1.59 | 3210 | 58.1 | 2.02 | 42.0 |
| H.W., 51 | LVH left outflow tract lesion | 180 | 68.3 | 1.82 | 3850 | 55.2 | 2.11 | 50.0 |
| H.H., 55 | HCVD | 177 | 69.5 | 1.85 | 3740 | 53.8 | 2.02 | 46.0 |
| L.C., 36 | RHD, MS | 173 | 70.0 | 1.82 | 4820 | 62.7 | 2.65 | 40.0 |
| L.S., 45 | Tbc. pericard. | 172 | 65.5 | 1.77 | 4280 | 65.4 | 2.42 | 31.0 |
| M.L., 53 | HCVD | 190 | 130.0 | 2.55 | 6480 | 49.0 | 2.55 | 51.0 |
| N.C., 52 | ASCVD | 178 | 84.2 | 2.02 | 4380 | 52.1 | 2.17 | 42.5 |
| S.J., 23 | RHD. Rheum. pericard. | 168 | 63.0 | 1.70 | 4100 | 65.2 | 2.41 | 47.0 |
| S.R., 65 | HCVD | 169 | 67.0 | 1.78 | 4600 | 59.7 | 2.58 | 38.0 |
| W.R., 30 | Hypertension with coarct. aorta | 173 | 75.5 | 1.89 | 4980 | 66.0 | 2.64 | 43.0 |
| | | | | | | | Avg. (17 pts.) = 2.37 ± 0.26 (S.D.) $p = 0.1$ | |

cardiovascular disease (ASCVD), rheumatic heart disease (RHD), and congenital heart disease (CHD).

*Group II* (8). This group consisted of cardiac patients who had previously been in congestive heart failure but who were now compensated following treatment in this hospital.

*Group III* (12). This group consisted of cardiac patients who had a history of dyspnea, orthopnea, paroxysmal nocturnal dyspnea and, when present, physical or x-ray evidence of pulmonary congestion.

*Group IV* (25). This group consisted of cardiac patients who had evidences of pulmonary congestion plus either two or more of the following: venous distention, enlarged liver, ascites, hydrothorax or peripheral edema.

*Group V* (4). This group consisted of patients who had primary pulmonary disease and secondary right ventricular hypertrophy plus either two or more of the following: venous distention, enlarged liver and peripheral edema.

A more complete description of the symptoms and findings of individual patients at the time of the blood volume determination may be found in tables 3 to 7.

## Results

The whole blood volumes in the normal patients were found to range from 2500 to 6084 cc. Volumes were also calculated as cubic

TABLE 4.—*Group II Consisted of Cardiac Patients Who Had Previously Been in Congestive Heart Failure, but Who Were Now Compensated Following Treatment in this Hospital*

| Group II Pt., Age | Diagnosis | Ht., cm. | Wt., Kg., dry | Surface area, sq.M., dry | Total Blood Vol., cc. | Blood Vol., cc./Kg., dry | Total Blood Vol., L./sq.M., dry | PCV |
|---|---|---|---|---|---|---|---|---|
| B.G., 75 | ASCVD | 168 | 63.5 | 1.72 | 4800 | 64.5 | 2.79 | 43.0 |
| B.L., 38 | RHD, AI, MI, MS | 172 | 67.5 | 1.80 | 4700 | 70.0 | 2.61 | 44.0 |
| B.H., 63 | ASCVD | 172 | 49.0 | 1.53 | 3540 | 72.2 | 2.31 | 48.5 |
| C.J., 82 | HASCVD | 187 | 85.0 | 2.10 | 5650 | 66.5 | 2.69 | 38.0 |
| H.C., 55 | Pulmon. emphysema, chr. cor pulmon. | 186 | 89.0 | 2.13 | 5900 | 66.3 | 2.77 | 61.0 |
| S.E., 64 | ASCVD | 168 | 52.3 | 1.59 | 3590 | 68.7 | 2.26 | 44.5 |
| S.F., 55 | ASCVD | 174 | 88.6 | 2.03 | 4710 | 53.2 | 2.32 | 58.0 |
| W.E., 47 | ASCVD | 169 | 73.2 | 1.83 | 5280 | 72.0 | 2.89 | 52.0 |
| | | | | | | Avg. (8 pts.) = 66.6 ± 9.1 cc./Kg. | | |

TABLE 5.—*Group III Consisted of Cardiac Patients Who Had a History of Dyspnea, Orthopnea, Paroxysmal Nocturnal Dyspnea and, When Present, Physical or X-ray Evidence of Pulmonary Congestion**

| Group III Pt., Age | Diagnosis | Ht., cm. | Wt., Kg. | | Surface area, sq.M. | | Total Blood Vol., cc. | Blood Vol., cc./Kg. | | Blood Vol., L./sq.M. | | PCV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | wet | dry | wet | dry | | wet | dry | wet | dry | |
| E.R., 78 | ASHD—acute myocard. infarct | 176 | 63.6 | 57.0 | 1.76 | 1.70 | 4140 | 65.0 | 73.6 | 2.34 | 2.43 | 33.0 |
| H.H., 69 | ASHD—old myocard. infarct | 173 | 68.0 | 64.5 | 1.80 | 1.77 | 4480 | 66.0 | 69.4 | 2.49 | 2.43 | 50.0 |
| H.R., 59 | ASHD | 172 | 53.6 | 50.5 | 1.62 | 1.58 | 3280 | 61.2 | 65.0 | 2.02 | 2.08 | 39.5 |
| J.J., 79 | ASHD—old myocard. infarct | 183 | 90.0 | 85.7 | 2.12 | 2.10 | 5180 | 57.6 | 60.4 | 2.44 | 2.46 | 46.0 |
| K.P., 66 | ASHD—old myocard. infarct | 173 | 66.0 | — | 1.78 | — | 3420 | 52.0 | — | 1.92 | — | 42.0 |
| M.D., 59 | HASCVD | 174 | 57.7 | 53.5 | 1.70 | 1.64 | 3980 | 66.4 | 74.4 | 2.34 | 2.42 | |
| N.M., 62 | HASCVD—AF | 170 | 65.1 | 62.5 | 1.76 | 1.72 | 4006 | 61.6 | 64.2 | 2.28 | 2.32 | 44.0 |
| R.D., 32 | RHD with MS, MI, AS, AI | 186 | 75.0 | 65.9 | 1.98 | 1.88 | 5250 | 70.0 | 78.7 | 2.64 | 2.79 | 34.0 |
| S.R., 64 | HCVD | 170 | 63.7 | — | 1.74 | — | 4260 | 67.0 | — | 2.45 | — | 49.0 |
| F.E., 51 | ASHD—recent | 180 | 86.5 | 83.5 | 2.06 | 2.04 | 5630 | 65.1 | 67.4 | 2.73 | 2.76 | 47.0 |
| F.L., 60 | ASHD—AF | 170 | 88.3 | 88.0 | 2.00 | 1.99 | 4340 | 49.2 | 49.3 | 2.17 | 2.18 | 46.0 |
| W.A., 69 | ASHD | 163 | 62.3 | 55.8 | 1.66 | 1.59 | 3242 | 52.1 | 58.2 | 1.95 | 2.04 | 44.0 |
| | | | | | Avg. (12 pts.) = | | | 61.0 ± 6.6 $p = 0.02$ | 66.0 ± 6.78 | 2.3 ± 0.28 $p = 0.3$ | 2.39 ± 0.25 $p = 0.3$ | |

* At the request of the editor, the details of the symptoms and findings are being omitted from this table. These will be furnished on request.

TABLE 6.—*Group IV Consisted of Cardiac Patients Who Had Evidences of Pulmonary Congestion Plus Either Two or More of the Following: Venous Distention, Enlarged Liver, Ascites, Hydrothorax or Peripheral Edema**

| Group IV Pt., Age | Diagnosis | Ht., cm. | Wt., Kg. | | Surface area, sq.M. | | Total Blood Vol., cc. | Blood Vol., cc./Kg. | | Blood Vol., L./sq.M. | | PCV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | wet | dry | wet | dry | | wet | dry | wet | dry | |
| B.C., 39 | Syph. HD. AI | 185 | 75.0 | 69.0 | 1.98 | 1.92 | 5560 | 74.0 | 80.7 | 2.81 | 2.90 | 43 |
| B.L., 38 | RHD, AI, MI, MS | 171 | 68.8 | 64.0 | 1.81 | 1.77 | 5540 | 80.4 | 86.5 | 3.06 | 3.13 | 41 |
| B.H., 63 | ASCVD | 171 | 55.7 | 48.0 | 1.63 | 1.58 | 4650 | 83.5 | 97.0 | 2.85 | 2.94 | 42 |
| C.T., 55 | RHD with MS. MI | 166 | 82.2 | 73.0 | 1.90 | 1.81 | 7400 | 90.0 | 101.0 | 3.89 | 4.08 | 50 |
| C.D., 66 | ASHD | — | 52.3 | 49.5 | — | — | 4590 | 87.6 | 92.6 | — | — | 44 |
| C.J., 82 | HASCVD | 186 | 89.5 | 77.0 | 2.15 | 2.05 | 5710 | 63.9 | 74.2 | 2.65 | 2.78 | 41 |
| C.T., 60 | ASCVD | 179 | 69.5 | | 1.88 | | 5920 | 85.0 | | 3.14 | | 50 |
| G.C., 60 | Syph. HD. AI | 165 | 57.3 | 52.0 | 1.61 | 1.58 | 4700 | 82.0 | 90.5 | 2.92 | 2.98 | 31 |
| H.C., 54 | HCVD. Malig. hyperten. | 183 | 61.0 | — | 1.80 | — | 4480 | 73.6 | — | 2.49 | — | 34 |
| H.L., 25 | RHD with MS, M.I. | 176 | 58.5 | 57.0 | 1.76 | 1.72 | 4410 | 75.4 | 77.4 | 2.50 | 2.68 | 50 |
| J.H., 56 | ASHD | 175 | 75.0 | 67.0 | 1.90 | 1.81 | 7030 | 94.0 | 105.0 | 3.7 | 3.88 | 47 |
| J.J., 80 | HCVD | 168 | 57.0 | 50.5 | 1.62 | 1.58 | 3543 | 62.3 | 70.4 | 2.19 | 2.14 | 36 |
| K.G., 56 | HASCVD—old myocard. infarct | 168 | 102.0 | 77.0 | 2.09 | 1.88 | 7380 | 72.5 | 96.0 | 3.53 | 3.93 | 52 |
| M.E., 68 | HASCVD—old myocard. infarct. | 168 | 73.3 | 64.0 | 1.81 | 1.71 | 4750 | 64.8 | 74.2 | 2.63 | 2.66 | 54 |
| P.R., 70 | HCVD | 170 | 80.0 | *died* | 1.91 | | 6210 | 77.7 | | 3.25 | | 40 |
| P.J., 66 | ASCVD | 175 | 51.3 | 51.0 | 1.61 | 1.61 | 4840 | 94.2 | 94.8 | 3.00 | 3.00 | 52 |
| R.C., 63 | RHD with MS, MD, AF | 175 | 99.5 | 81.6 | 2.14 | 1.97 | 8730 | 87.7 | 107.0 | 4.07 | 4.43 | 33 |
| R.J., 75 | ASCVD, AF | 166 | 72.0 | 65.2 | 1.82 | 1.78 | 6780 | 94.0 | 104.0 | 3.72 | 3.80 | 45 |
| S.G., 70 | ASCVD—old myocard. infarct | 166 | 61.8 | 53.0 | 1.72 | 1.61 | 4480 | 71.0 | 84.5 | 2.61 | 2.78 | 42 |
| S.J., 56 | ASCVD | 176 | 85.8 | 80.0 | 2.03 | 1.97 | 6300 | 73.5 | 78.8 | 3.11 | 3.20 | 49 |
| T.E., 49 | ASHD with old myocard. infarct | 174 | 109.0 | 96.4 | 2.22 | 2.10 | 7950 | 73.0 | 82.5 | 3.58 | 3.78 | 43 |
| W.E., 47 | ASCVD | 170 | 82.0 | 72.5 | 1.92 | 1.82 | 5550 | 68.0 | 76.5 | 2.89 | 3.05 | 46 |
| T.F., 61 | ASCVD | 178 | 68.1 | 64.5 | 1.84 | 1.80 | 5300 | 63.4 | 77.5 | 2.72 | 2.78 | 38 |
| U.C., 86 | ASCVD | 177 | 57.0 | 54.5 | 1.70 | 1.67 | 4120 | 72.0 | 75.5 | 2.42 | 2.48 | 48 |
| H.F., 60 | Old myocard. infarct | 183 | 82.6 | 68.7 | 2.04 | 1.90 | 6442 | 78.0 | 93.7 | 3.15 | 3.29 | 60 |
| | | | | | Avg. (25 pts.) = | | | 77.7 ± 0.95 $p$ = >0.01 | 88.7 ± 11.2 $p$ = >0.01 | 3.04 ± 0.46 $p$ = >0.01 | 3.17 ± 0.56 $p$ = >0.01 | |

* At the request of the editor, the details of the symptoms and findings are being omitted from this table. These will be furnished on request.

centimeters per kilogram and liters per square meter of body surface area of the individual (table 2). When calculated on a basis of weight the range was 45.8 to 77.6 cc. per kilogram with a mean of 65.5 cc. per kilogram and a standard deviation of ±5.95 cc. per kilogram. On the basis of square meters of body surface there was a range of 1.79 to 3.05 liters per square meter, a mean of 2.49 and a standard deviation of 0.28 liters per square meter.

In cardiac patients who had never been in congestive heart failure (group I) and in recently compensated cardiac patients (group II) blood volumes were within the normal range. Normal values were also found in patients with pulmonary congestion alone (group III). Blood volumes were significantly elevated in the majority of patients who had venous distention, liver congestion, and peripheral edema whether secondary to left ventricular failure or mitral stenosis (group IV) or to primary pulmonary disease (group V). The individual determinations in these groups of cardiac patients are compared with the normal range and mean in figure 2. The values for blood volume in cubic centimeters, cubic centimeters per kilogram and liters per square meter for each patient in the five groups are listed in tables 3 to 7.

A statistical comparison* of each group of

* The statistical comparisons of the several groups were made as follows:

$$\text{Variance of } V = \frac{dev^2 \text{ of group } I \pm dev^2 \text{ of group } II}{N_1 \pm (N_2 - 2)}$$

$$\text{To calculate standard error of difference} = \frac{V}{N_1} \pm \frac{V}{N_2}.$$

$$t \text{ was calculated as} = \frac{\text{difference between means}}{\text{standard error of difference}}$$

TABLE 7.—*Group V Consisted of Patients Who Had Primary Pulmonary Diseases, Secondary Right Ventricular Hypertrophy Plus Either Two or More of the Following: Venous Distention, Enlarged Liver and Peripheral Edema**

| Group V Pt., Age | Diagnosis | Ht., cm. | Weight, Kg. | | Surface area, sq.M. | | Total Blood Vol., cc. | Blood Vol., cc./Kg. | | Blood Vol., L./sq.M. | | PCV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | wet | dry | wet | dry | | wet | dry | wet | dry | |
| B.F., 57 | Pulmon. emphysema. Chr. cor pulmon. | 175 | 56.0 | 49.0 | 1.68 | 1.59 | 4720 | 84.2 | 96.4 | 2.80 | 2.96 | 55.0 |
| H.C., 55 | Pulmon. emphysema. Chr. cor pulmon. | 188 | 101.0 | 88.0 | 2.28 | 2.15 | 7700 | 76.2 | 87.5 | 3.37 | 3.48 | 51.0 |
| T.R., 38 | Pulmon. emphysema. Chr. cor pulmon. | 175 | 57.4 | 51.4 | 1.70 | 1.62 | 4730 | 83.0 | 92.2 | 2.78 | 2.92 | 54.5 |
| W.F., 42 | Bronchiect. Pulmon. emphysema. Chr. cor pulmon. | 171 | 51.6 | 44.5 | 1.60 | 1.50 | 4430 | 86.0 | 99.5 | 2.76 | 2.95 | 55.0 |
| | | | | | Avg. (4 pts.) = | | | 82.2 ±7.64 | | 2.93 ±0.42 | 3.07 ±0.19 | |

* At the request of the editor the details of the symptoms and findings are being omitted from this table. These will be furnished on request.

TABLE 8.—*Comparative Mean Values of Blood Volumes in Normal and Cardiac Patients by Weight and Surface Area*

| | Normals (88) | Group I (17) | Group II (8) | Group III (12) | Group IV (25) | Group V (4) |
|---|---|---|---|---|---|---|
| Wet, cc./Kg. | | 61.3 ± 7.6 | 66.6 ± 9.1 | 61.0 ± 6.6 | 77.7 ± 9.5 | 82.2 ± 7.6 |
| Dry, cc./Kg. | 65.5 ± 5.95 | — | — | 66.1 ± 6.8 | 88.7 ± 11.2 | 94.8 ± 11.5 |
| Wet, L./sq.M. | | 2.37 ± 0.26 | 2.58 ± 0.27 | 2.31 ± 0.28 | 3.04 ± 0.46 | 2.93 ± 0.42 |
| Dry, L./sq.M. | 2.49 ± 0.28 | — | — | 2.39 ± 0.25 | 3.17 ± 0.56 | 3.07 ± 0.19 |

Values obtained for wet weight were calculated from the actual weight at the time of the blood volume determination. Values for dry weight were calculated from the weights obtained at the time of maximum compensation.

cardiac patients with normal subjects revealed the following results:

Patients in group I had blood volumes significantly lower than the volumes of normal subjects when the volumes were calculated as cubic centimeters per kilogram ($p = 0.01$) and probably significantly lower than the volumes of normal subjects when the values were calculated as liters per square meter of body surface area ($p = 0.1$).

Patients of group II did not have blood volumes significantly different from the values of normal subjects when determined either as cubic centimeters per kilogram or as liters per square meter.

The blood volumes of patients in group III were significantly lower than those of normal subjects when calculated as cubic centimeters per kilogram ($p = 0.02$) but were almost the same as normal when calculated from "dry" weight. When these same comparisons were made on a basis of liters per square meter of body surface area the blood volume was lower than the blood volume of normal subjects "wet" ($p = 0.03$) but not significantly lower, "dry" ($p = 0.3$).

Blood volumes of patients in group IV were very significantly higher than the volumes in normal subjects whether calculated as cubic centimeters per kilogram or liters per square meter "wet" or "dry" ($p$ in each case less than 0.01).

Although there were only four patients in group V the comparison was higher than

normal when determined either as cubic centimeters per kilogram or liters per square meter of body surface area "wet" or "dry" ($p = 0.01$). The comparison of the mean values and standard deviation in each of these groups with the values in normal subjects is made in table 8.

## Discussion

Elevated blood volumes in these patients apparently depended upon the development of right ventricular failure, whether it occurred as a result of left ventricular failure, mitral stenosis or primary pulmonary disease. This was true on comparison by weight or by body surface area. Greater accentuation of these differences was evident when calculating the congestive heart failure patient's blood volumes by the lowest weight following cardiac compensation; i.e., dry weight (see table 4).

In patients who manifested only signs and symptoms of left ventricular failure or mitral stenosis (group III), not a single blood volume determination was elevated above that of subjects in the normal group. Although five of the patients in group IV had blood volumes within the range of the mean and standard deviation of subjects in the normal group, in only one of these did the volume remain in this range when volumes were calculated by dry weight. On the basis of these studies we believe that in the fully developed picture of congestive heart failure, that is, pulmonary and hepatic congestion, venous distention and edema, the blood volume is significantly elevated, but that in a few patients in this state it may be normal. The explanation of the findings of a normal blood volume in such a patient with right and left heart failure is not clear to us.

Serial determinations were done on 16 patients with symptoms and signs of right and left ventricular failure. In general, blood volumes reverted to normal values as cardiac reserve returned; the converse was true in patients who became clinically worse or died.

Although part of the increased blood volume in congestive failure due to cor pulmonale may be explained by secondary polycythemia, serial determinations on these patients after cardiac therapy revealed a return toward the normal ranges.

Our results were in general in accord with Nylin and Hedlund[16] who stated that in congestive heart failure the increase in whole blood volume is most marked in patients with severe edema and slight in those with pulmonary congestion alone.

These results are not in agreement with those of Prentice and associates[19] who found normal blood volumes in 12 of 27 patients with heart failure. The explanation of these findings which differ from ours evidently is not that their patients had predominantly left ventricular failure, for they state that only one third of the patients with normal volumes had left sided failure. If the majority of their patients had only minimal to moderate edema this may be significant since the degree of elevation of blood volume in our cases was roughly correlated with the amount of edema and excess body weight. Nor does our data support the finding of these authors that most of their patients who did have elevated blood volumes in heart failure were those with old rheumatic heart disease and that those with hypertensive and arteriosclerotic heart disease had essentially normal volumes. We found elevated blood volumes in most of the patients with concomitant left and right sided failure regardless of the etiology of the heart disease. Like ourselves, Prentice and co-workers[19] found normal blood volumes in their patients with only left ventricular failure. As they state, however, there were no cases of early acute left ventricular failure in their study. We were unable to test patients with left ventricular failure until 12 to 18 hours after hospital admission; however, these patients still had signs and symptoms of failure at the time of testing.

Differences in the blood volume of normal subjects and patients with left ventricular failure from those with combined right and left failure depend to a large extent upon the correct evaluation of the patients and their proper placement in the groups as described. Certainly there is no sharp clinical division between left and right failure. Fluid retention, hepatic congestion and elevated venous pressure

during exercise may exist and may not be clinically recognized in cardiac patients. Venous pressure and circulation time often add little to this differentiation. In most instances the clinician can separate patients who have predominantly left heart failure from those with both left and right or right failure alone. Concomitant cardiac catheterization and renal studies would add greatly to the interpretation of blood volume changes.

The chain of events in the development of expanded intravascular volumes in cardiac failure has always been a controversial subject and often has been compared to the "horse and cart" problem. Needless to say the complete picture may stem from the concept of insufficient cardiac output relative to the metabolic needs of an individual. Not only are there changes resulting from poor output but there are also changes resulting from an increasing residual of blood proximal to the failing ventricle. In left ventricular failure and mitral stenosis reduced output (resulting in relative anoxia) to the organs such as the kidney, liver, and endocrine glands may result in changes such as salt and water retention. Apparently from our studies this retention does not result in hypervolemia if there is left ventricular failure or mitral stenosis alone but apparently depends upon the failure of the right ventricle as well. As Ross[20] and others have pointed out, there may be a shift of a portion of the total circulating blood volume to the pulmonary vascular tree without a resultant increase in the total circulating blood volume. This shift into the pulmonary vascular tree is probably dependent upon an adequately functioning right ventricle relative to the left ventricle. The dyspnea, orthopnea, and pink frothy sputum occurring with left ventricular failure and mitral stenosis are probably due to this relative shift. Clinically these symptoms may disappear or lessen with the onset of right ventricular failure and mitral stenosis and this may be due to this relative shift. Consequently we feel that hypervolemia occurring only with right ventricular failure plays a definite role in the sequence of the pathologic physiology of the failing heart.


## Summary

1. The advantages and method of using radiochromium are described for determining whole blood volume in normal and congestive heart failure patients.

2. Patients with normal heart function were observed to have whole blood volumes of 65.5 ± 5.95 cc. per kilogram or 2.49 ± 0.28 liters per square meter of body surface area.

3. Hypervolemia occurs in the majority of cardiac patients with signs and symptoms of right ventricular failure but not in those cardiac patients with left ventricular insufficiency or mitral stenosis alone.

## Sumario Español

1. Las ventajas y el método de usar radiochromio se describen para la determinación del volumen sanguíneo total en sujetos normales y en pacientes en decompensación cardíaca.

2. Pacientes con función cardíaca normal fueron observados tener volumenes sanguíneos total de 65.5 ± 5.95 cc. por kilogramo o 2.49 ± 0.28 litros por metro cuadrado de superficie del cuerpo.

3. Hipervolemia ocurre en la mayoría de los pacientes cardíacos con signos y síntomas de decompensación del ventrículo derecho pero no en aquellos pacientes cardíacos con insuficiencia ventrícular izquierda o estenosis mitral solamente.


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# The Origin of Aortic Phospholipid in Rabbit Atheromatosis

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Radioactive phosphorus ($P^{32}$) was injected into normal and cholesterol-fed rabbits. A marked derangement of aortic phospholipid metabolism was found in the cholesterol-fed animals. The phospholipid found in the atheromatous aortas appeared to have been synthesized by the aorta itself rather than to have been deposited there from the plasma.

THE etiology of atheromatosis has been explored from different points of view.[1, 2, 3] Blood cholesterol has been investigated intensively and found elevated in a portion of the patients and in all experimental animals developing this condition. Plasma phospholipids are usually elevated when the cholesterol level is high. Some workers, however, have related the increased cholesterol-phospholipid ratio to the development of atheromata. More recently attention has been focused on "physical hyperlipemia," that is, the presence of abnormal lipoproteins and exaggerated chylomicronemia in the plasma of atherosclerotics.

The increased cholesterol and phospholipid content of the atheromatous aorta was noted long ago. More recently Buck and Rossiter studied the fatty materials of plaques in fresh human aortas and reported that phospholipids, and, in particular, sphingomyelins constituted an important part of the plaque lipids.[4] Chernick and co-workers[5] have reported that the normal rat aorta is capable of synthesizing fatty acids and phospholipids in vitro but further relation of this observation to the mechanism of atherogenesis was not made.

In the present investigation we have attempted to evaluate the role of plasma and aorta phospholipids in rabbit atheromatosis. Analysis of specific activity data obtained from phospholipid molecules labeled with radioactive phosphorus revealed a major disturbance in the phospholipid metabolism of the rabbit aorta when atheromata are present.

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## Methods

White New Zealand rabbits were fed 100 Gm. of Purina Rabbit Chow per day. In the experimental animals, the Purina diet was supplemented with 1 Gm. of cholesterol* and 2.8 Gm. of Humko vegetable fat per day for a period of five months. The total fat content of the experimental diet amounted to 5.3 per cent, as compared to 2.5 per cent for the normal diet. At the end of the five-month period 0.5 millicuries of radioactive phosphate ($P^{32}$) was administered intravenously to control and experimental animals. Blood samples were taken from each animal two, four and six hours after injection. At the six-hour interval the animals were sacrificed and the liver and thoracic aorta were removed for analysis. Plasma and tissues were analyzed for phospholipid $P^{32}$ and $P^{31}$ by extracting twice for two hours with ethanol at 60 C. The tissue residue was subjected to an overnight Soxhlet extraction with ethyl ether, and subsequently the alcohol-ether extract was taken almost to dryness in vacuo under a carbon dioxide atmosphere. The phospholipids were re-extracted with petroleum ether, and $P^{32}$ and $P^{31}$ were determined in this extract. Where acid-soluble inorganic and organic phosphates were determined, separate tissue aliquots were homogenized in 5 cc. of 20 per cent trichloroacetic acid. After centrifugation, the supernatant liquid was removed and the inorganic and organic acid soluble phosphates were separated by precipitation with magnesium.[6] Aortic cholesterol was determined by the method of Sperry and Webb.[7]

## Results

The analytic data are given in table 1. Liver phospholipid concentrations in the experimental animals were not elevated significantly above control levels, but plasma and aortic

* Kindly donated in part by Merck and Company.

TABLE 1.—*Lipids and Acid Soluble Phosphates in Aorta, Liver, and Plasma*

| | | Number of Animals | | Mean ± S.E.* | | Per cent Increase Over Control |
|---|---|---|---|---|---|---|
| | | Cont. | Chol.-Fed | Control | Cholesterol-Fed | |
| Rabbit Wt. (Kg.) | | 6 | 9 | 2.6 ± 0.1 | 2.9 ± 0.1 | 12 |
| Whole Thoracic Aorta (Gm.) | | 6 | 9 | 0.55 ± 0.09 | 0.90 ± 0.10 | 64 |
| Per cent Phospholipid§ | Aorta | 6 | 9 | 0.542 ± 0.030 | 1.12 ± 0.079 | 106 |
| | Liver | 6 | 9 | 3.13 ± 0.10 | 3.59 ± 0.17 | 15 |
| | Plasma | 6 | 9 | 0.073 ± 0.004 | 0.368 ± 0.064 | 404 |
| Lipid per Whole Thoracic Aorta (mg.) | Total Lipid | 6 | 9 | 24.7 ± 4.2 | 89.4 ± 9.1 | 262 |
| | Cholesterol | 6 | 9 | 0.746 ± 0.133 | 27.0 ± 4.8 | 3520 |
| | Phospholipid | 6 | 9 | 2.84 ± 0.33 | 10.5 ± 1.7 | 270 |
| Inorganic P. Specific Activity × $10^3$‡ | Liver | 7 | 9 | 116 ± 7.95 | 155 ± 28.1 | 33.6 |
| | Aorta | 3 | 4 | 55.6 ± 18.7 | 51.0 ± 4.72 | −8.27 |
| Organic Acid Sol. P. Specific Activity × $10^3$‡ | Liver | 7 | 9 | 62.6 ± 6.55 | 60.1 ± 5.40 | −3.99 |
| | Aorta | 4 | 4 | 64.4 ± 15.6 | 58.2 ± 3.27 | −9.62 |
| Phospholipid Specific Activity × $10^3$‡ | Liver | 6 | 9 | 8.05 ± 0.47 | 12.1 ± 1.7 | 50 |
| | Aorta | 6 | 9 | 5.98 ± 1.00 | 10.6 ± 1.8 | 77 |
| | Plasma | 6 | 9 | 4.80 ± 0.81 | 4.17 ± 0.62 | −13 |
| Per cent of Inj. $P^{32}$ in Phospholipid of Entire Thoracic Aorta × $10^3$ | | 6 | 9 | 0.673 ± 0.131 | 4.39 ± 1.00 | 552 |

* S.E. = Standard error.

‡ Specific activity expressed as the percentage of the injected $P^{32}$ per milligram of phosphorus.

§ Phospholipid P × 25, per 100 Gm. fresh tissue.

phospholipid concentrations were increased 400 per cent and 100 per cent, respectively. The total amount of phospholipid in the whole thoracic aorta was actually about four times greater in the cholesterol-fed animals than in the control animals. Although the total aortic cholesterol was increased by an even greater amount, the data emphasize that phospholipids constitute a significant portion of the plaque. If the entire increase in aortic lipid was due to the presence of fatty plaques, phospholipids account for 14 per cent of the plaque lipid.*

The $P^{32}$ data in table 1 are the means of specific activities, which are calculated as the percentage of the administered $P^{32}$ in the phospholipid fraction per milligram of phospholipid phosphorus. This quantity is a relative measure of the percentage renewal of phospholipid molecules provided the cholesterol feeding does not alter the rate of incorporation of $P^{32}$ into the phospholipid precursors. Apparently cholesterol feeding did not affect these precursors, for the specific activities of the inorganic and organic acid-soluble phosphates of the liver and aorta are essentially the same in the experimental and control animals.

The data in table 1 indicate that the specific activity of liver phospholipids was not greatly affected by the cholesterol feeding. In contrast, the amount of radioactive phospholipid per cubic centimeter of plasma (specific activity times concentration) was five times as large in the cholesterol-fed animals as in the controls. Since all plasma phospholipids are presumably derived from the liver,[8] it must be

* This may not be entirely correct since some increase in adventitial fat may occur in the cholesterol-fed animals.

concluded that in the cholesterol-fed rabbits the exchange between liver and plasma phospholipids is accelerated. This observation does not confirm the findings of Perlman and co-workers,[9] who observed that the administration of cholesterol to rats depressed the appearance of radioactive phospholipids in liver and plasma.

In the aortas of the experimental animals an even more pronounced stimulation of phospholipid synthesis was observed (bottom row table 1). Comparison of the specific activity data does not adequately express the great increase in the turnover of these phospholipids since the amount of the phospholipids in the thoracic portion of atheromatous aortas was four times as great as in the normal aortas. But the percentage of the injected $P^{32}$ present in the phospholipids of the entire aorta indicates an increase in phospholipid synthesis of perhaps five to six fold. The comparison of the specific activities of the phospholipids in the aorta, plasma, and liver in table 2 shows that the specific activity of these lipids in the aorta of a few of the high cholesterol animals is even greater than the specific activity of the liver, which is normally the most active phospholipid synthesizing tissue in the body. In all instances the specific activity of the phospholipids in the aorta is much higher than the average or terminal specific activity of plasma phospholipids. This observation strongly suggests that the major portion of the phospholipids in the atheromatous plaque is synthesized in situ rather than being derived from plasma phospholipids or plasma lipoproteins.

One might object that an alternate explanation of the data is possible. Our results by themselves might be compatible with deposition of plasma phospholipids if the aorta were able to remove selectively one plasma phospholipid component having a specific activity not only considerably higher than that of the total plasma phospholipids but also exceeding the specific activity of the combined aortic phospholipid. It would be very difficult to rule out this possibility completely, since there might conceivably be present in plasma a particular lipoprotein of very high specific activity. However, the studies of Turner and co-workers[10] indicate that the range of phospholipid specific activities in the lipoproteins of human plasma is rather narrow. In addition, our own data* on the specific activity of plasma lecithin, cephalin and sphingomyelin of atherosclerotic rabbits have indicated that none of these fractions have sufficient $P^{32}$ to account for the high specific activity of aortic phospholipids on the basis of deposition.

TABLE 2*—*Specific Activities of Aorta, Liver, and Plasma Phospholipids*

| Animal | Type | Specific Activity × $10^3$ | | | |
|---|---|---|---|---|---|
| | | Liver | Aorta | Plasma | |
| | | | | Average | Terminal |
| E | N. | 8.69 | 3.38 | 0.948 | 3.04 |
| F | N. | 9.50 | 4.70 | 1.60 | 4.93 |
| P | N. | 8.79 | 9.80 | 2.96 | 8.41 |
| R | N. | 6.30 | 4.14 | 1.26 | 3.58 |
| T | N. | 7.60 | 5.92 | 1.86 | 3.44 |
| U | N. | 7.43 | 7.94 | 1.70 | 5.40 |
| Average | | 8.05 | 5.98 | 1.72 | 4.80 |
| S.E. | | 0.47 | 1.00 | 0.28 | 0.81 |
| C | C.F. | 17.8 | 24.0 | 0.953 | 2.91 |
| D | C.F. | 21.8 | 9.68 | 1.47 | 5.54 |
| G | C.F. | 10.2 | 7.98 | 0.983 | 4.03 |
| H | C.F. | 8.62 | 8.80 | 1.92 | 6.98 |
| J | C.F. | 7.14 | 10.4 | 1.36 | 4.58 |
| K | C.F. | 10.4 | 8.18 | 1.28 | 4.42 |
| N | C.F. | 14.5 | 10.5 | 0.917 | 3.04 |
| O | C.F. | 10.1 | 7.49 | 1.03 | 2.79 |
| S | C.F. | 8.20 | 8.30 | 0.975 | 3.24 |
| Average | | 12.1 | 10.6 | 1.21 | 4.17 |
| S.E. | | 1.7 | 1.8 | 0.11 | 0.62 |

* See footnote accompanying table 1.
C.F. = Cholesterol Fed. N. = Normal.

## DISCUSSION

The observation that the amount of phospholipid in the whole thoracic aorta of the cholesterol-fed rabbit is four times as great as in control animals confirms the findings of Weinhouse and Hirsch in the rabbit[11] and of Buck and Rossiter in human autopsy material[4] that phospholipids constitute an appreciable fraction of the newly developed atheromatous

* Unpublished preliminary observations.

plaques. The similarity in composition of the early plaques to the lipid pattern of plasma has prompted the idea that the lipids in the plaque are derived from the plasma lipids. This theory has received support from the recent discovery that certain individuals with a tendency toward atherosclerosis show the presence of excessive amounts of abnormal lipoproteins in plasma. Even though no direct proof is available, the possibility that these abnormal lipoproteins might be the precursors of atheromatous deposits has been recognized. Our studies in the rabbit, however, give a different interpretation to the presence of large amounts of phospholipids in the atheromatous deposits. It appears that the atherosclerotic rabbit has acquired the ability to synthesize large amounts of phospholipids in the aorta. The observation that the specific activity of the phospholipids in the atheromatous plaques is much higher than the average specific activity of the plasma phospholipids over a period of six hours, excludes the possibility that an appreciable fraction of the plaque's phospholipids was derived from the lipoproteins in the bloodstream.

The relation of these observations to the process of atherogenesis in rabbits has suggested two theories: (1) The atheromatous plaque, that is, the cholesterol *and* phospholipid, are both derived from a local derangement of the lipid metabolism in the aorta. The abnormal blood lipoproteins are not the cause, but the result of a similar derangement of lipid metabolism in the liver. (2) The cholesterol in the plaque is derived from the blood plasma, but the phospholipids are synthesized by the aorta. This possibility appears to be supported by the findings of Biggs and Kritchevsky who observed that orally-administered labeled cholesterol is found in the plaque of rabbits whereas labeled water is not converted to cholesterol in the artery.[12]

A possible role of plasma phospholipids in keeping cholesterol in solution has been postulated by many workers.[1, 3] One might similarly speculate that the accelerated phospholipid synthesis by the aorta is an attempt to solubilize the cholesterol in the atheromatous plaque, or a reflection of the intense activity of the granulomatous inflammation as it reacts to cholesterol.

Whatever interpretation is put on the data obtained in the cholesterol-fed rabbits, our findings indicate that these animals suffer from an alteration in the metabolism of the aorta. The mechanism of atherogenesis in man might be elucidated if a similar situation could be discovered in the human artery. Our preliminary studies on human arteries have indicated that radioactive phospholipids do accumulate there after $P^{32}$ administration.


## Summary

The incorporation of radioactive phosphorus ($P^{32}$) in the liver, plasma, and aorta phospholipid of cholesterol-fed and normal rabbits has been measured. Increased amounts of phospholipids were found in the plasma and aorta of the cholesterol-fed animals. Phospholipids in the atheromatous aortas were synthesized five times as fast as in the normal aortas. The major amount of the plaque's phospholipid appeared to be synthesized by the aorta, rather than derived from plasma. The bearing of these findings on atherogenesis is discussed.



## Acknowledgment

The authors are indebted to Florence Blevins, Lovell Lawrence, and Frances Carpenter for their assistance with the analyses.



## Sumario Español

La incorporación de fósforo radioactivo ($P^{32}$) en el higado, plasma y la fosfolipina de la aorta en conejos alimentados con colesterol ha sido determinada. Cantidades aumentadas de fosfolipinas fueron encontradas en el plasma y la aorta de los animales alimentados con colesterol. Las fosfolipinas en las aortas ateromatosas fué sintetizada cinco veces más rapidamente que en las aortas normales. La mayor porción de la fosfolipina en placas aparentemente fue sintetizada por la aorta en lugar de ser derivada del plasma. El significado de estos hallazgos en cuanto a la aterogenesis se discute.


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# The Effect of Prolonged Sodium Depletion and of Hydrallazine Hydrochloride and Hexamethonium Bromide on the Digital Vascular Resistance in Primary Hypertension

*By* GERALD H. EURMAN, M.D., AND MILTON MENDLOWITZ, M.D.

The effect of dietary sodium depletion and of oral hydrallazine hydrochloride and parenteral hexamethonium bromide on the digital circulation was studied by repeated measurements of pressure and flow before and after inhibition of sympathetic nerve discharge in a small series of hypertensive patients. Sodium depletion had no demonstrable effect on neurogenic digital vasoconstriction but produced either a decrease in intrinsic digital vascular resistance, a decrease in intrinsic flow, or both. The chief effect of the drugs studied, in contrast, was elimination of neurogenic digital vasoconstriction.

SODIUM depletion is known to decrease the blood pressure of some patients with primary hypertension.[1, 2] In order to study the mechanism of this effect, arterial blood pressure, blood flow and vascular resistance in the digital circulation were measured before and after inhibition of sympathetic nerve discharge. These studies were carried out in 13 hypertensive patients on low-sodium diets. Although the results were similar in all these cases only five are reported here because urinary electrolyte controls were available in these cases only. The results were contrasted with a similar investigation before and after the administration of hexamethonium bromide and hydrallazine hydrochloride in two hypertensive patients and hydrallazine hydrochloride alone in two hypertensive patients. One of the latter patients was studied both during dietary and, subsequently, during drug therapy.

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## METHOD

Digital blood pressure was measured with a Gaertner capsule,[3] a metal cylinder lined with an inflatable rubber cuff. The finger is blanched by rolling a rubber band from the tip of the finger to the base, and the Gaertner capsule encircling the middle phalanx is inflated above systolic pressure. The rubber band is cut and the capsule gradually deflated. Systolic pressure is the point at which flushing appears in the fingertip and diastolic pressure, the point of cessation of throbbing.[4] Both points are checked three to five times.

Blood flow was measured calorimetrically,[5] using the Fick principle to determine blood flow to digital skin. Instead of oxygen, heat is used to measure flow. In this technic the finger is inserted into an insulated covered cup containing water, a Beckman thermometer, and a mechanical rotary stirrer. The temperature of the stirred water, initially set at 6 to 7 C. below mouth temperature, is read every minute from the thermometer as heat is transferred from finger to the water. When the temperature rise becomes relatively constant, the average minute increment for three minutes is used for the determination. To this value is added the fall in the calorimeter temperature, when a cork replaces the finger, as representative of the temperature loss from the calorimeter to the room.

The venous blood temperature in the finger during the three-minute study period is assumed to be equal to the mean calorimeter water temperature, whereas the arterial blood temperature is assumed to approximate mouth temperature. Both these assumptions have been shown to be valid by direct thermo-

TABLE 1.—*The Effect of Dietary Sodium Depletion on the Digital Circulation in Hypertension*

| Patient | Date | Dietary Na per day *mEq.* | Na & Cl in urine *mEq./day* | Brachial B.P. *mm. Hg.* | Digital B.P. *mm. Hg.* | Digital Blood Flow *cc./cm.²/min.* | Vascular Volume Index *cu. microns/ cm.² skin* |
|---|---|---|---|---|---|---|---|
| | | | | Before (B) and after (A) Sympathetic Inhibition* | | | |
| S. R. | 3-30-51 | ca. 170 | | B 226/130 | | | |
| 36 | | 3 wks. | | A 184/132 | 168/136 | 0.35 | 450 |
| F | | | | | | | |
| | 1-23-52 | Av. 17 | Na 12 | B 190/120 | 142/115 | 0.25 | 388 |
| | | 4 wks. | Cl 22 | A 150/100 | 105/ 80 | 0.28 | 604 |
| | 3-5-52 | 4 | Na 0.7 | B 170/105 | 140/100 | 0.19 | 319 |
| | | 1 wk. | Cl 1.6 | A 132/ 80 | 120/ 98 | 0.35 | 641 |
| | 4-10-52 | 4 | Na 4.6 | B 180/100 | 150/ 94 | 0.19 | 310 |
| | | 6½ wks. | Cl 12.4 | A 162/100 | 130/ 92 | 0.31 | 556 |
| R. C. | 1-8-52 | 30 | | B 205/140 | 195/170 | 0.12 | 128 |
| 48 | | 3 wks. | | A 170/120 | 145/112 | 0.22 | 348 |
| M | | | | | | | |
| | 1-17-52 | 30 | | B 210/135 | 168/155 | 0.12 | 142 |
| | | 4 wks. | Cl 40 | A 174/118 | 128/118 | 0.23 | 369 |
| | 4-8-52 | 4 | Na 1 | B 205/115 | 145/ 95 | 0.14 | 226 |
| | | 9 wks. | Cl 4 | A 170/ 98 | 135/ 98 | 0.26 | 441 |
| D. W. | 12-14-51 | 30 | | B 150/100 | 140/120 | 0.14 | 214 |
| 46 | | 2 wks. | | A 135/110 | 140/100 | 0.26 | 425 |
| F | 12-21-51 | 30 | | | | | |
| | | 3 wks. | | B 150/105 | 140/130 | 0.24 | 339 |
| | | | | A 155/130 | 130/120 | 0.28 | 434 |
| | 3-10-52 | 4 | Na 0.5 | B 140/105 | 115/100 | 0.22 | 410 |
| | | 10 wks. | Cl 4 | A 130/100 | 95/ 88 | 0.22 | 475 |
| | 4-2-52 | 4 | Na 0.7 | B 132/ 98 | 110/ 90 | 0.17 | 334 |
| | | 14 wks. | Cl 13 | A 115/100 | 90/ 80 | 0.18 | 416 |
| L. S. | 2-5-52 | 30 | | B 230/125 | 140/ 95 | 0.18 | 318 |
| 56 | | 4 wks. | | A 230/130 | 160/110 | 0.28 | 412 |
| M | | | | | | | |
| | 2-28-52 | 30 | | B 230/130 | 150/ 85 | 0.22 | 351 |
| | | 7 wks. | | A 225/130 | 125/ 80 | 0.29 | 546 |
| | 4-7-52 | 4 | Na 4 | B 225/130 | 150/105 | 0.15 | 225 |
| | | 5 wks. | Cl 9 | A 165/115 | 125/ 65 | 0.20 | 415 |
| | 5-9-52 | 4 | Na 12 | B 170/105 | 115/ 72 | 0.22 | 459 |
| | | 9 wks. | Cl 24 | A 168/110 | 95/ 75 | 0.24 | 568 |
| | 5-21-52 | 4 | Na 4 | B 150/ 95 | 118/ 45 | 0.18 | 439 |
| | | 11 wks. | Cl 8 | A 155/100 | 100/ 50 | 0.22 | 600 |
| J. W. | 2-26-52 | 30 | | B 260/150 | 210/160 | 0.23 | 245 |
| 54 | | 3 wks. | | A 244/144 | 205/140 | 0.35 | 393 |
| M | | | | | | | |
| | 3-8-52 | 30 | | B 240/145 | 180/145 | 0.23 | 278 |
| | | 5 wks. | | A 235/140 | 160/115 | 0.34 | 494 |
| | 4-10-52 | 4 | Na 6 | B 200/105 | 125/ 80 | 0.19 | 380 |
| | | 5 wks. | Cl 12 | A 185/110 | 130/ 95 | 0.25 | 443 |
| | 4-23-52 | 4 | Na 2 | B 198/125 | 150/105 | 0.15 | 236 |
| | | 7 wks. | Cl 4 | A 188/112 | 135/ 95 | 0.20 | 352 |
| | 5-19-52 | 4 | Na 4 | B 220/120 | 170/110 | 0.06 | 86 |
| | | 11 wks. | Cl 6 | A 230/125 | 150/100 | 0.26 | 421 |

* Heat and tetraethylammonium chloride were used in all cases except for J. W. where heat alone was administered.

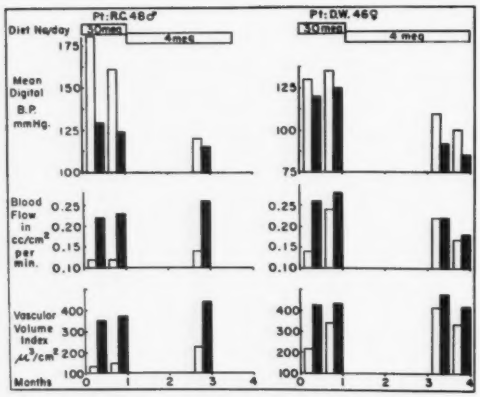


FIG. 1. Response to Low-Sodium Diet. The open bars indicate measurements made prior to sympathetic inhibition and the solid bars those made during sympathetic inhibition. The increase in caliber produced by sympathetic inhibition, as reflected by the difference in vascular volume indexes, represents the neurogenic component of the vasoconstriction. The index during sympathetic inhibition reflects the intrinsic or non-neurogenic structure and tone of the blood vessels with dietary sodium depletion. R. C. exhibited an increase in vascular caliber. D. W. exhibited a decrease in digital skin blood flow. No significant effect is evident in the neurogenic component of the vasoconstriction.

couple measurements after inhibition of sympathetic nerve discharge.[6] Before such inhibition the assumptions are valid provided the room temperature is maintained at 27 C. or more.[7] The total number of calories delivered in one minute divided by the arteriovenous blood temperature difference and the area of immersed skin, represents blood flow in cubic centimeters per square centimeter per minute. Corrections are made for the specific heat and specific gravity of blood and the hydrothermic equivalent of the apparatus.[5]

In each of the observations reported here, measurement of digital blood pressure and flow were made prior to, and after, the inhibition of sympathetic nerve discharge. The preliminary measurements were made at room temperature of 28 C. ± 1 degree. Sympathetic nerve discharge was inhibited by heating the trunk with an electric bulb cradle baker.[7] This inhibition was supplemented by the administration intravenously of 5 mg. per kilogram of tetraethylammonium chloride[9] in seven cases, and 0.8 mg. per kilogram of a quaternary amine, 2,6-dimethyl-1,1-diethyl piperidinum bromide (SC-1950)* [10] in one case. In one other case heat alone was used. Arnott and Macfie[11] have demonstrated that, in the skin of the digits, indirect heat alone inhibits sympathetic nerve discharge completely. The drugs were used to supplement the effect of indirect heat and especially to prevent reflex and psychic "breakthrough."[12]

The flow-pressure ratio multiplied by a constant is expressed as vascular volume index.[13] Flow is expressed in cubic centimeters per second and pressure (arithmetic mean) in dynes per square centimeter. The constant, $\eta$, is blood viscosity in dyne seconds per square centimeter. The index is measured in cubic microns. It is preferred because it is a rectilinear function of successive increments in flow at any given pressure, whereas resistance is curvilinear, approaching infinity with decreasing flow. Vascular volume index is a reciprocal of resistance and is directly proportional to the caliber of the blood vessels. The increase in caliber produced by sympathetic inhibition is considered representative of the neurogenic component of the vasoconstriction. The caliber *after* sympathetic inhibition is considered representative of the intrinsic or non-neurogenic structure and tone of the blood vessels.

The first set of studies was performed after three to seven weeks on control diets containing 30 mEq. of sodium daily, as analyzed by ashing and flame photometry. One patient's control study was performed while he was receiving a standard hospital diet. Each patient was then placed on a low-sodium diet and restudied at intervals, after 1 to 14 weeks. The low-sodium diet consisted of either a standardized (Kempner)[1] rice-fruit diet or a special low-sodium diet[2b] containing less than 4 mEq. of sodium in the daily ration. No patient was considered to be on a low-sodium regimen unless the urinary sodium and chloride were below 4 and 12 mEq. per day respectively. The drugs, employed for one to six-week therapeutic trials before each study, were oral hydrallazine hydrochloride* [14] and parenteral hexamethonium bromide.† [15]

## RESULTS

Table 1 presents the significant data in all the cases studied with respect to the effect of the sodium restricted diets on the digital circulation, and figure 1 demonstrates two cases graphically. There are two major effects of the diet. In two cases the calculated intrinsic (or non-neurogenic) vascular volume was increased, whereas in two other cases the only effect was a decrease in intrinsic blood flow, vascular caliber remaining comparatively unchanged. A combination of these two effects was observed in one case. The average random variation in the same individual of repeated measurements of blood flow or vascular volume

* Furnished by G. D. Searle and Co., Chicago, Ill.

* Furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J., as Apresoline.

† Furnished by E. R. Squibb and Sons, New Brunswick, N. J., as Bistrium.

index under these conditions is ±10 per cent. This is documented in earlier studies[4] as well as in numerous subsequent observations including the control studies presented here. The extent of the downward trend observed in flow or the upward trend in vascular volume index is therefore beyond that to be expected from chance fluctuations. The neurogenic component of the vasoconstriction fluctuated with great lability as was evident in the blood flow and vascular volume measurements prior to sympathetic inhibition. It was not significantly affected by the diet.

Table 2 presents the data from cases studied on drugs, and figure 2 demonstrates two such cases graphically. Hydrallazine, alone or combined with parenteral hexamethonium bromide, inhibited the neurogenic component in

TABLE 2.—*The Effects of Drug Therapy on the Digital Circulation in Hypertension*

| Patient | Date | Drug | Daily Dosage | Dietary Na per day *mEq.* | Brachial B.P. *mm. Hg.* | Digital B.P. *mm. Hg.* | Digital Blood Flow *cc./cm.²/min.* | Vasc. Vol. Index *cu. microns/cm.²/skin* |
|---|---|---|---|---|---|---|---|---|
| | | | | | Before (B) and after (A) Sympathetic Inhibition* | | | |
| R. C. | 6-5-52 | Phenob. | 30 mg. q.i.d. | 9 | B 210/142 | 185/100 | 0.26 | 356 |
| 29 | | | | | A 164/126 | 160/ 70 | 0.33 | 563 |
| F | | | | | | | | |
| | 6-10-52 | Phenob. | 30 mg. q.i.d. | 9 | B 194/138 | 145/ 54 | 0.30 | 582 |
| | | | | | A 164/126 | 150/ 52 | 0.34 | 657 |
| | 7-29-52 | Phenob. | 30 mg. q.i.d. | 9 | B 174/130 | 142/ 55 | 0.40 | 807 |
| | | Hpz | 50 mg. q.i.d. | | A 172/130 | 135/ 60 | 0.42 | 844 |
| | | C-6 | 45 mg. q.i.d. | | | | | |
| | 8-5-52 | Hpz, C-6 } Placebo | — | 9 | B 204/135 | 180/ 75 | 0.28 | 450 |
| | | | | | A 175/140 | 160/ 60 | 0.33 | 619 |
| I. B. | 10-15-52 | None | — | 9 | B 184/110 | 170/110 | 0.27 | 283 |
| 38 | | | | | A 135/ 88 | 155/100 | 0.35 | 555 |
| F | | | | | | | | |
| | 10-23-52 | Hpz | 50 mg. t.i.d. | 9 | B 150/100 | 115/ 70 | 0.33 | 712 |
| | | C-6 | 10 mg. b.i.d. | | A 130/ 88 | 110/ 56 | 0.30 | 750 |
| | 10-29-52 | Hpz, C-6 } Placebo | — | 9 | B 180/106 | 170/120 | 0.15 | 188 |
| | | | | | A 130/ 80 | 157/ 94 | 0.40 | 619 |
| R. C. | 1-8-52 | None | — | 30 | B 205/140 | 195/170 | 0.12 | 128 |
| 48 | | | | | A 170/120 | 145/112 | 0.22 | 348 |
| M | 1-17-52 | None | — | 30 | B 210/135 | 168/155 | 0.12 | 142 |
| | | | | | A 174/118 | 128/118 | 0.23 | 369 |
| | 4-22-52 | Hpz | 50 mg. q.i.d. | 4 | B 167/ 92 | 128/ 90 | 0.26 | 473 |
| | | | | 14 wks. | A 146/ 78 | 117/ 89 | 0.27 | 527 |
| | 5-1-52 | Hpz | 50 mg. q.i.d. | 30 | B 178/ 95 | 158/ 92 | 0.34 | 528 |
| | | | | 1 wk. | A 175/ 86 | 146/ 85 | 0.35 | 598 |
| C. B. | 3-3-52 | None | — | 30 | B 220/135 | 158/122 | 0.19 | 277 |
| 65 | | | | | A 210/135 | 124/ 80 | 0.23 | 441 |
| M | | | | | | | | |
| | 4-22-52 | Hpz | 125 mg. q.i.d. | 30 | B 175/110 | 110/ 65 | 0.32 | 743 |
| | | | | | A 200/125 | 113/ 70 | 0.32 | 698 |
| | 4-30-52 | Hpz | 150 mg. q.i.d. | 30 | B 199/114 | 112/ 80 | 0.28 | 566 |
| | | | | | A 200/125 | 107/ 76 | 0.30 | 650 |
| | 5-21-52 | Hpz | 100 mg. q.i.d. | 30 | B 205/110 | 118/ 65 | 0.23 | 516 |
| | | | | | A 165/100 | 98/ 58 | 0.24 | 617 |

* Heat and tetraethylammonium chloride were used in all the cases except for I. B. where heat and SC-1950 was administered.

Phenob. = phenobarbital; Hpz = hydrallazine hydrochloride (1-hydrazinophthalazine); C-6 = hexamethonium.

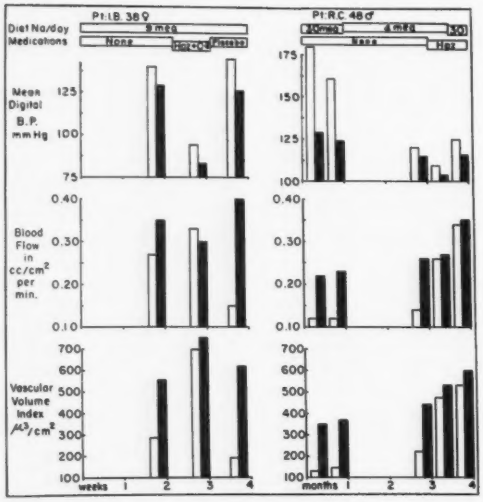


FIG. 2. Response to Hypotensive Drugs. Notations same as in figure 1. Hpz = hydrallazine hydrochloride (1-hydrazinophthalazine). C-6 = hexamethonium bromide. I. B. received a diet containing 9 mEq. of sodium throughout the study. R. C. received both the rice and control diet while 1-hydrazinophthalazine was administered during each. While on drug therapy both patients exhibited an increase in blood flow before sympathetic inhibition as well as an increase in intrinsic vascular caliber. Note the approximation of vascular caliber values before and after sympathetic inhibition, while the patients were receiving medications. This indicates a decrease in the neurogenic component of each patient's hypertension during the drug treatment period.

every case. This was manifested by the failure of indirect heat and ganglionic blockade to produce any further increase in vascular caliber as measured by the vascular volume index. In addition, the drugs appeared to increase intrinsic vascular caliber as well, although part of this effect might have been caused by associated dietary salt depletion, at least in two of the cases.

## DISCUSSION

Dietary sodium depletion in these studies either increased the intrinsic (non-neurogenic) caliber of the blood vessels or decreased the intrinsic blood flow as measured in the digital circulation. The decreases in brachial blood pressure were roughly proportional to these effects. The low-sodium regimen did not affect the neurogenic component of digital vasoconstriction. This seems in accord with the suggestion of Perera and Blood[16] "that vasoconstrictive factors (at least in part neurogenic) in hypertensive patients are independent of those alterations in peripheral resistance influenced by sodium chloride . . . ." Their tentative conclusion was drawn from the observation that after salt restriction a "patient's ability to respond to autonomic or neurogenic stimuli is unaffected" as was manifest in "an absence of correlation between 'resting' and 'casual' blood pressure readings . . . ."

In contrast, the effect of the two drugs in decreasing the neurogenic component of the digital skin circulation is similar to some of their demonstrated actions on other parts of the systemic circulation.[17-19] In the digits, however, the neurogenic factor is exaggerated, probably because of the large number of arteriovenous anastomoses which are under sympathetic nervous control.[20] Hence, inhibition by drugs of neurogenic vasoconstriction is more striking in the digital than in the systemic circulation as a whole.

## SUMMARY AND CONCLUSIONS

Digital arterial pressure, blood flow and vascular resistance were measured repeatedly before and after inhibition of sympathetic nerve discharge in eight patients with hypertension. The effects of dietary sodium depletion were evaluated in five patients and the effects of hydrallazine hydrochloride and hexamethonium bromide, in the remaining three and in one of the preceding five.

Although broad statistical conclusions cannot be drawn from this series of cases, the low-sodium regimen, in the cases studied, increased intrinsic digital vascular caliber, decreased intrinsic digital blood flow, or did both without producing any significant or consistent effect on the neurogenic component of the vasoconstriction. In contrast the major effect of either hydrallazine hydrochloride alone or in combination with hexamethonium bromide was inhibition of neurogenic digital vasoconstriction, although some increase in intrinsic digital vascular caliber was also produced.

### Acknowledgments

We are grateful to Miss Shirley English and Mrs. Joan Dayton for technical assistance.

### Sumario Español

El efecto de la depleción del sodio dietético y de la administración oral del clorhidrato de hydrallazine y administración parentérica de bromuro de hexamethonium en la circulación digital fué estudiado por medio de repetidas determinaciones de presión y circulación antes y después de la inhibición de descargas de nervios simpáticos en una serie pequeña de pacientes hipertensos. Depleción del sodio no tuvo efecto demostrable alguno en la vasoconstricción digital neurológica pero produjo o un decremento en resistencia digital vascular intrínseca, o un decremento en circulación intrínseca, o ambos.

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# Total Urinary Catechol Excretion in Cardiovascular and Other Clinical Conditions

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Although colorimetry (method of Shaw) permits neither a differentiation of epinephrine and norepinephrine nor their separation from other catechols, it reveals the total urinary catechol excretion, including those portions which were inactivated in the body. No significant abnormalities were found in arterial hypertension, in congestive heart failure, after myocardial infarction and during emotional stress. Thoracolumbar sympathectomy depressed total catechol excretion temporarily. In renal uremia, the regularly demonstrable elevation of the blood catechols was paralleled by a diminution of the conjugated catechols in the urine. It appears to be due to renal retention.

THE increasing appreciation of the pathogenic importance of sympathoadrenal neurosecretion in cardiovascular pathology has prompted various attempts to gage the state of function of the sympathetic nervous system and of the adrenal medulla by means of assay of epinephrine, norepinephrine and related compounds in the urine. Holtz and co-workers[1] detected increased amounts of pharmacodynamically active catecholamines in the urine of 16 out of 23 patients with arterial hypertension. This was confirmed by Kroneberg and Schümann[2] but Goldenberg and Rapport[3] recorded abnormally high values in only 2 out of 14 patients with essential hypertension.

The colorimetric test of Shaw[4] permits the isolation and recovery of all chromogenic catechol compounds.[5] It reveals the presence in the urine of chromogenic material far in excess of what can be assumed to be the combined amounts of active epinephrine, norepinephrine and hydroxytyramine.[2, 6, 7] In addition, acid hydrolysis intensifies the color reaction markedly.[2, 6] It has been concluded, therefore, that the urine contains, beside the active material, considerable quantities of both free and conjugated derivatives of deaminated epinephrine and norepinephrine with an intact catechol nucleus.

Using the colorimetric assay of total catechols in the nonhydrolyzed and hydrolyzed urines of normal and hypertensive individuals, Kroneberg and Schümann[2] did not observe any difference between the two groups regarding the nonconjugated chromogenic catechols but the conjugated catechols, as recovered by hydrolysis, appeared to be markedly augmented in the hypertensive group (average +73 per cent). Nuzum and Bischoff[6] did not confirm the latter finding. In their series, no significant difference was apparent in the urines of normal and hypertensive subjects. Only in three patients with myocardial infarction did they observe an increased ratio of the readings from hydrolyzed and nonhydrolyzed urine.[6]

Shaw's so-called "specificity test" (color ratio of alkali- and acid-treated specimens), upon which Nuzum and Bischoff[6] based their calculation of the absolute amounts of excreted epinephrine, is not suitable for the differentiation of epinephrine and norepinephrine since it applies to both substances.[8, 9] Moreover, the difference in color intensity yielded by epinephrine and norepinephrine (4.4 parts norepinephrine equalling 1 part epinephrine), and the uncertainty regarding the degree of chromogenicity of the other participating (deaminated ?) catechol compounds in the urine impair the conclusiveness of the "specificity" ratio.

In the following, we shall report the total color readings obtained in nonhydrolyzed and

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hydrolyzed urine specimens of normal individuals and of patients with cardiovascular diseases and other clinical conditions.

## Methods

In most instances, the urine specimens were collected over 12-hour periods (from 7 p.m. to 7 a.m.) in vessels which contained sodium bisulfite (about 10 per cent) for stabilization of the catecholamines. Following the procedure described by Kroneberg and Schümann,[2] the urine volumes were brought up to 1000 cc. with distilled water. Ten cc. of the diluted urine were again diluted with 80 cc. of distilled water. Two cc. of this second dilution were placed in each of two test tubes for further analysis with the modified method of Shaw, as described in detail elsewhere,[10] using epinephrine standards which were kept constant with a Coleman photoelectric colorimeter. To another 10 cc. of the first dilution (the pH of which had been determined), 0.2 cc. of concentrated sulfuric acid was added, followed by hydrolysis in a boiling water bath for 15 minutes. Subsequently, the original pH was restored through addition of an appropriate amount of 30 per cent sodium hydroxide. Now one part of the hydrolyzed urine was likewise diluted with eight parts of distilled water, and 1 cc. was placed in each of the test tubes to be processed colorimetrically in the same way as the nonhydrolyzed samples. Three parallel determinations (three test tubes) were made for the nonhydrolyzed and for the hydrolyzed urines, respectively. The amounts of nonconjugated and total (nonconjugated plus conjugated) catechols, excreted in 12 hours and expressed in milligram epinephrine color equivalents (number of milligrams of epinephrine giving identical color effect), were calculated by multiplying the number of color units, read from the standard curve, with 0.008 for nonhydrolyzed and 0.016 for hydrolyzed urine.

In model tests, the chromogenicity of neither epinephrine nor norepinephrine was significantly altered by the process of hydrolysis. The supernatant fluid over the alkaline aluminum hydroxide adsorbates of nonhydrolyzed urine samples contained chromogenic material which was not present in the supernatant fluid of equally prepared adsorbates from hydrolyzed urine. Thus, it appears that hydrolysis had made previously conjugated and therefore unadsorbable catechols suitable for adsorption and colorimetry.

Neither the addition of the preservative nor allowing the specimens of urine to stand at room temperature for as long as 24 hours caused any significant alteration of the colorimetric results.

## Results

(a) *Under Normal Conditions.* One hundred and fifty-nine tests, carried out on the night urines of 69 hospitalized normotensive patients in whom no major abnormality of sympathoadrenal function was suspected, yielded values which corresponded rather closely to 29 analo-

Table 1.—*Catechol Excretion in 12-Hour Night Urine Specimens*

| Type of Cases | No. Subjects | No. Specimens | Nonhydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Hydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Ratio of Hydrolyzed to Nonhydrolized Urine (Avg. and Range) |
|---|---|---|---|---|---|
| Normal students | 29 | 29 | 2.1(0.9–3.4) | 5.0(1.6–9.7) | 2.4(1.0–4.0) |
| Normotensive hospitalized patients | 69 | 159 | 2.2(0.2–11.2) | 4.4(0.4–19.2) | 2.0(1.0–7.8) |
| Hypertension, group I (bl. pr. 170/100 and above) | 16 | 52 | 2.8(0.6–15.3) | 5.2(1.5–17.0) | 1.9(1.0–4.8) |
| Hypertension, group II (bl. pr. 150/90 to 170/100) | 15 | 27 | 2.8(0.8–6.4) | 4.5(0.9–11.2) | 1.6(1.0–2.7) |
| Recent myocardial infarction | 5 | 16 | 3.9(0.9–9.6) | 6.7(1.5–15.6) | 1.7(1.0–5.0) |
| Congestive cardiac failure | 12 | 32 | 2.3(0.4–7.4) | 3.6(0.6–9.7) | 1.6(1.3–2.9) |
| Pregnancy (6th to 9th month) | 9 | 13 | 2.0(0.6–6.1) | 3.7(1.0–6.8) | 1.9(1.1–6.7) |
| Panhypopituitarism | 3 | 19 | 0.7(0.4–1.2) | 1.0(0.4–1.8) | 1.4(1.0–3.0) |

Table 2.—*Day and Night Catechol Excretion by Hospitalized Patients*

| Time | No. Subjects | No. Specimens | Nonhydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Hydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Ratio of Hydrolyzed to Nonhydrolyzed Urine (Avg. and Range) |
|---|---|---|---|---|---|
| 7 a.m. to 7 p.m. | 10 | 34 | 2.5(0.5–4.6) | 5.3(1.2–12.0) | 2.1(1.1–5.0) |
| 7 p.m. to 7 a.m. | 10 | 34 | 2.7(0.7–6.3) | 5.2(0.7–13.4) | 1.9(1.1–5.0) |

TABLE 3.—*Catechol Excretion by Normal Students at Ease and under Emotional Tension*

| Situation | No. Subjects | No. Specimens | Nonhydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Hydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Ratio of Hydrolyzed to Nonhydrolyzed Urine (Avg. and Range) | Morning Blood Pressure (Avg.) | Morning Heart Rate (Avg.) |
|---|---|---|---|---|---|---|---|
| 12-hour night specimens | | | | | | | |
| Midsemester | 29 | 29 | 2.1(0.9–3.4) | 5.0(1.6–9.7) | 2.4(1.0–4.0) | 117/70 | 102 |
| Night before exam | 29 | 29 | 2.7(1.0–5.1) | 5.7(1.3–9.6) | 2.1(1.2–3.7) | 129/75 | 112 |
| 4-hour forenoon specimens | | | | | | | |
| Midsemester | 14 | 14 | 1.0(0.6–1.7) | 2.3(0.7–4.1) | 2.3(1.1–3.0) | 115/69 | 69 |
| During exam | 14 | 14 | 1.0(0.6–2.5) | 2.1(0.9–3.9) | 2.1(1.3–4.0) | 128/75 | 82 |

gous tests done on the night urines of 29 healthy students (table 1).

(b) *Day and Night Values.* No significant difference was found between the day and night catechol excretion in 34 tests on 10 hospitalized individuals (table 2).

(c) *Effect of Emotional Tension.* In 29 medical students, the urinary catechol excretion during the night preceding an examination did not differ significantly from that observed in midsemester (table 3). Neither did tests on 14 students show any difference between the excretion during four-hour periods which were filled with written examinations, and that during corresponding four-hour periods on ordinary class days (table 3); blood pressure and heart rate, on the other hand, were significantly elevated immediately before the examinations.

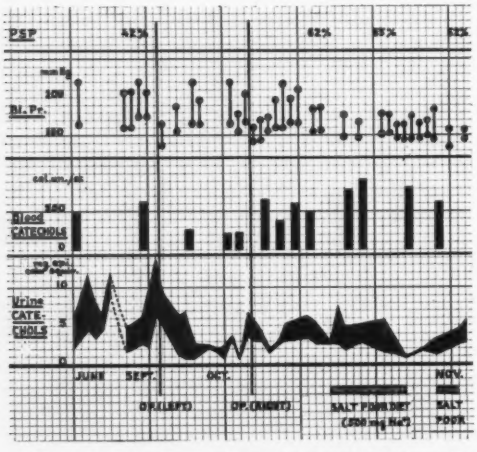


FIG. 1. Case E. B. Essential hypertension. Bilateral sympathectomy. Follow-up of PSP tests; blood pressure levels; blood catechol concentrations; urinary catechol excretion (night urine specimens). The lower contour represents the nonhydrolyzed, the upper contour the hydrolyzed urine readings; thus the width of the black band indicates the amount of conjugated catechols.

(d) *Findings in Arterial Hypertension* (table 1). Fifty-two tests were carried out on the night urines of 16 hospitalized patients with moderate to severe but uncomplicated hypertension (blood pressure from 170/100 up) and 27 tests on the night urines of 15 patients with mild hypertension (150/90 to 170/100). There were no significant differences in catechol excretion between these two hypertensive groups, nor between the hypertensive and the normotensive groups. In cases in which tests were carried out repeatedly, the day-to-day variations proved considerable, both among normotensive and hypertensive individuals. (See fig. 1.)

(e) *Effect of Thoracolumbar Sympathectomy.* Twelve-hour night specimens were taken from two hypertensive women before operation, after left thoracolumbar sympathectomy, and later after additional right thoracolumbar sympathectomy (fig. 1 and table 4). In case F. R., only hydrolyzed urine samples were tested. Significant diminutions of the average catechol excretion were observed following left sympathectomy in both cases, but in the period following the final contralateral operation no further diminution of the readings was noted. In case F. R., the values even returned to and above the preoperative level. The blood

TABLE 4.—*Urine-, Blood- and Sympathetic Tissue Catechols in Two Sympathectomized Hypertensive Patients*

| Cases | Clinical Phases | No. Specimens | Night Urine Catechols | | No. Specimens | Blood Catechols | Sympathetic Tissue Catechols | | Blood Pressure (mm. Hg) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nonhydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Hydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | | c.u./cc* (Avg. and Range) | Section of Sympathetic | c.u./Gm.† | Systolic | Diastolic |
| E. B., ♀, 39 yrs. | Before operation | 9 | 4.0(1.6–9.2) | 8.2(2.8–13.4) | 2 | 226(198–255) | — | — | 212–240 | 120–150 |
| | After l. sympath. | 10 | 1.9(0.7–4.3) | 4.1(0.7–9.2) | 3 | 92(85–100) | Left | 3111 | 130–240 | 75–134 |
| | After r. sympath. | 17 | 2.3(0.9–3.0) | 4.3(1.1–7.5) | 8 | 264(152–370) | Right | 301 | 115–235 | 75–132 |
| F. R., ♀, 49 yrs. | Before operation | 13 | — | 3.4(2.5–4.8) | 7 | 216(142–270) | — | — | 200–240 | 100–158 |
| | After l. sympath. | 8 | — | 2.3(0.4–3.1) | 2 | 273(246–300) | Left | 2740 | 160–220 | 104–130 |
| | After r. sympath. | 9 | — | 3.6(1.6–5.1) | 4 | 235(205–285) | Right | 242 | 122–176 | 80–108 |
| | 6 mos. later | 2 | — | 4.2(3.8–4.5) | — | — | — | — | 138–145 | 86–90 |

* Color units (each = 0.001 microgram epinephrine) per cc.
† Color units (each = 0.001 microgram epinephrine) per gram.

TABLE 5.—*Total Urinary Catechol Excretion during Infusion of Epinephrine and Norepinephrine. Two Studies on Same Volunteer*

| Duration of Urine Sample Collection | Material Infused (micrograms) | Vol. of Urine Specimens (cc.) | Hydrolyzed Urine Catechols (Microgram Epinephrine Color Equivalents) | | Total Amounts Catecholamines Infused |
|---|---|---|---|---|---|
| | | | Per cc. Urine | Per Hour | |
| *min.* | | | | | |
| 60 | Saline | 36 | 1.7 | 61 | |
| 60 | Saline | 34 | 0.9 | 34 | |
| 15 | Epinephrine 186 | 80 | 0.6 | 109 | Epinephrine 0.93 mg. (930 microgram epinephrine color equivalents) |
| 15 | Epinephrine 186 | 50 | 0.6 | | |
| 15 | Epinephrine 279 | 15 | 0.7 | | |
| 15 | Epinephrine 279 | 14 | 1.5 | | |
| 60 | — | 27 | 2.0 | 45 | |
| 60 | — | 47 | 1.6 | 75 | |
| 60 | — | 50 | 0.9 | 45 | |
| 60 | Saline | 104 | 0.7 | 73 | |
| 30 | Norepinephrine 372 | 40 | 0.8 | 45 | Norepinephrine 1.86 mg. (425 microgram epinephrine color equivalents) |
| 30 | Norepinephrine 372 | 35 | 0.4 | | |
| 30 | Norepinephrine 558 | 70 | 0.2 | 27 | |
| 30 | Norepinephrine 558 | 65 | 0.2 | | |
| 60 | — | 24 | 1.1 | 26 | |
| 60 | — | 70 | 0.6 | 42 | |
| 60 | — | 45 | 0.9 | 41 | |
| 60 | — | 50 | 0.7 | 35 | |

catechol concentrations varied rather widely both before and after the operations without showing any postoperative downward trend, except temporarily in case E. B. (fig. 1).

In both patients F. R. and E. B. the removed sympathetic tissue was colorimetrically examined (table 4). The two first removed left sympathetics contained 2,740 and 3,111 color units (each unit equalling 0.001 microgram of epinephrine) per gram, respectively,

while the later removed right sympathetic tissue contained only 242 and 301 color units per gram, respectively. Thus, the last removed sympathetic tissues contained in both cases approximately 90 per cent less catechols than their earlier extirpated counterparts.

(f) *Effect of Infusions of Epinephrine and Norepinephrine.* On two different days, a normal volunteer received intravenous infusions of epinephrine (0.93 mg.) and norepinephrine (1.86 mg.) over periods of one and two hours, respectively. The urine was collected by catheter (table 5). During the epinephrine infusion, the catechol excretion was slightly increased; during the infusion of norepinephrine, on the other hand, it appeared to be diminished.

(g) *Findings in Uremia.* In 10 patients with uremia and high blood catechol concentrations (table 6), a total of 28 night urine specimens was examined. The average amount of catechols recovered from the nonhydrolyzed urines was only slightly below the normal average but that from the hydrolyzed urines was about 25 per cent below normal.

(h) *Findings after Recent Myocardial Infarction.* In five cases of myocardial infarction, 16 twelve-hour night urine specimens were collected on the days on which the infarctions occurred and/or during the following few days (table 1). The readings were high in one case but near normal in the others.

(i) *Findings in Congestive Heart Failure.* In 12 patients with congestive heart failure (32 tests) the nonhydrolyzed urines gave a normal average reading; the average reading of the hydrolyzed specimens was slightly below normal (table 1).

(j) *Influence of Pregnancy.* In nine women in the sixth to ninth month of pregnancy, the values were not significantly different from those found in nonpregnant women (table 1).

(k) *Influence of Hypopituitarism.* In nine tests on three patients, the catechol excretion was consistently subnormal (table 1).

## Discussion

In accordance with the findings of Nuzum and Bischoff,[6] the statement of Kroneberg and Schümann[2] that the ratio of hydrolyzed to nonhydrolyzed catechols is increased in the urine of hypertensive individuals could not be confirmed. We did not find any significant difference between the urines of normotensive persons (hospitalized and nonhospitalized) on the one hand, and those of mildly or severely hypertensive patients on the other, except

Table 6.—*Total 12-Hour Night Urine- and Blood Catechols in Renal Uremic Patients*

| Case No. | N.P.N.† mg% | No. Urine Specimens | 12-Hour Night Urine Catechols | | | Blood Catechols c.u./cc.* |
|---|---|---|---|---|---|---|
| | | | Nonhydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Hydrolyzed Urine (Avg. and Range) (Mg. Epinephrine Color Equivalents) | Ratio of Hydrolyzed to Nonhydrolyzed Urine (Avg. and Range) | |
| 1 | 178 | 4 | 2.0(1.1–4.3) | 2.5(1.1–5.3) | 1.3(1.0–1.7) | 648 |
| 2 | 100 | 4 | 1.8(0.9–2.6) | 4.3(2.0–6.8) | 2.2(1.6–2.6) | 375 |
| 3 | ? | 3 | 2.9(1.0–4.0) | 4.9(1.8–7.9) | 1.7(1.4–2.0) | 305 |
| 4 | 120 | 1 | 2.0(2.0–2.0) | 2.0(2.0–2.0) | 1.0(1.0–1.0) | 388 |
| 5 | 195 | 2 | 0.7(0.5–0.9) | 0.8(0.8–0.9) | 1.3(1.0–1.6) | 430 |
| 6 | 150 | 1 | 0.8(0.8–0.8) | 0.8(0.8–0.8) | 1.0(1.0–1.0) | 324 |
| 7 | ? | 3 | 0.7(0.0–1.8) | 1.1(0.0–2.8) | 1.6(1.5–3.5) | 780 |
| 8 | 86 | 6 | 1.8(1.1–3.4) | 3.4(1.6–7.8) | 1.7(1.0–2.3) | 480 |
| 9 | 120 | 2 | 3.8(2.5–5.1) | 6.1(4.5–7.8) | 1.7(1.5–1.8) | 360 |
| 10 | 100 | 2 | 2.1(0.8–3.4) | 3.1(0.9–5.3) | 1.4(1.1–1.6) | 470 |
| Total..... | | 28 | 1.9(0.0–5.1) | 3.2(0.0–7.9) | 1.7(1.0–2.6) | 456 |
| Normal..... | | 159 | 2.2(0.2–11.2) | 4.4(0.4–19.2) | 2.0(1.0–7.8) | 200 |

* Color units (each = 0.001 microgram epinephrine) per cc.

† Nonprotein nitrogen.

perhaps a slight augmentation of the non-hydrolyzed catechols in the latter groups.

We do not believe that our essentially negative findings disprove the possibility of an increased sympathogenic secretion of norepinephrine into the cardiovascular muscular tissue in arterial hypertension and in states of emotional excitement. A substantial portion of the locally discharged catecholamines is probably destroyed right on the spot and the amounts of active sympathomimetic catecholamines which can be assumed to be responsible for the clinical cardiovascular tone at a given time form only a small fraction of the total catechols excreted in the urine. Their fluctuations may be easily overshadowed by the bulk of pharmacodynamically inactive chromogenic compounds. Norepinephrine, because of its relatively weak color intensity, is particularly unlikely to markedly influence the total color readings.

Only about 10 per cent of infused epinephrine were colorimetrically recovered in the urine during the infusion while infused norepinephrine could not be demonstrated at all in the specimens collected during and within four hours after the infusion. These results are not surprising since it was found by Bacq[11] that infused epinephrine is rapidly stored by the tissues and then again slowly but only partially released so that free active epinephrine appears in the urine only in small quantities within an hour after infusion. Conjugated inactive epinephrine is excreted even more slowly. Not more than 5 per cent were recovered over a period of eight hours. The excess output of active norepinephrine during intravenous infusion of this catecholamine, as observed by von Euler and Luft,[12] was only 1.5 to 2.5 per cent of the infused quantity. Thus, the time element, as well as enzymatic destruction of part of the sympathomimetic catechols in the body, constitute additional factors of uncertainty in attempts to evaluate adrenosympathetic neurosecretory activity by the determination of total urinary catechol excretion.

The markedly reduced catechol concentration in the sympathetic nerve tissue, excised two weeks after contralateral sympathectomy, suggests the possibility that after removal of major sections of sympathetic nervous tissue, the remaining portions of the sympathetic nervous system intensify their catechol-discharging activity at the expense of their reserves, thus maintaining a more or less undiminished total catechol output, even though from differently distributed areas, possibly including the brain.[13] The relatively uncharacteristic behavior of the blood and urine catechols would seem to be consistent with this hypothesis.

Our observations on patients with recent myocardial infarction and with congestive heart failure do not suggest any specific abnormalities of catechol excretion. The same can be said of pregnancy. The markedly subnormal catechol excretion in hypopituitarism, a condition which is usually accompanied by postural hypotension, may constitute an analogy to the low excretion of norepinephrine and epinephrine which was observed by Luft and von Euler[14] in patients with orthostatic hypotension.

In 10 renal uremic patients, the colorimetric urine readings suggested an impairment of excretion, especially of the conjugated (hydrolyzed) catechols. This is of interest insofar as it seems to explain the regularly observed elevation of the blood catechol concentration in uremia[15] and the resulting "false positive" benzodioxane and Regitine tests in such patients.[16, 17, 18]

## Summary

In 530 urine specimens, obtained from 169 subjects (usually for the period of 7 p.m. to 7 a.m.), the total catechol excretion was determined colorimetrically by the method of Shaw. Since part of the catecholamines, secreted by the adrenal medulla and by the sympathetic nerves, is probably destroyed in the body, and since the urine readings include large portions of pharmacodynamically relatively inactive catechol compounds, the colorimetric results do not present a clear quantitative picture of the neurosecretory discharges of pharmacodynamically active norepinephrine and epinephrine at a given time. Part of the latter substances is excreted in a sulfoconjugated, inactive, but colorimetrically re-

coverable, form. A differentiation of epinephrine and norepinephrine by means of the Shaw method is not possible, contrary to statements which have appeared in the literature.

No regularly or grossly abnormal total catechol excretions were observed in patients with arterial hypertension, congestive heart failure or myocardial infarction, or in persons in a state of emotional tension. There was no significant difference between day and night excretion. In three patients with hypopituitarism, the catechol excretion was markedly subnormal.

Infusion of epinephrine increased the total catechol readings only slightly; infused norepinephrine could not be detected in the urine by colorimetry.

Unilateral thoracolumbar sympathectomy was followed by a transient diminution of the urinary catechols, but this was not further accentuated by subsequent contralateral sympathectomy. The catechols of the sympathetic tissue, obtained at the second operation, and compared with the first excised tissue, appeared to be reduced by 90 per cent in two patients examined. This suggests that after partial sympathectomy there is a compensatory overdischarge from the remaining sympathetic elements.

In uremic patients, the excretion of the conjugated catechols was significantly diminished. This is consistent with the regular and characteristic finding of elevated, presumably retained, blood catechols in renal uremia.


## Sumario Español

En 530 especimenes de orina obtenidos en 169 sujetos (usualmente en el período de 7 p.m. a 7 a.m.), la excreción total de catecol fué determinada calorimetricamente por el método de Shaw. Como parte de las catecolaminas, secretadas por la médula adrenal y por nervios simpáticos, es probablemente destruída en el cuerpo y como las lecturas en las orinas incluyen grandes porciones de relativamente inertes farmaco-dinamicamente compuestos de catecol, los resultados calorimetricos no representan un cuadro cuantitativo claro de las descargas neurosecretorias de norepinefrina o epinefrina farmaco-dinamicamente activa en un tiempo dado. Parte de las substancias últimas son excretadas en formas sulfoconjugadas, inactivas, pero calorimetricamente recobrables. Una diferenciación entre epinefrina y norepinefrina por medio del método de Shaw no es posible, contrario a manifestaciones que han aparecido en la literatura.

Las excreciones de catecol total observadas en pacientes con hipertensión arterial, decompensación cardíaca o infartos del miocardio, o en personas en estados de tensión emocional, no fueron regularmente o crasamente anormales. No hubo diferencia significativa entre la excreción diurna o nocturna. En tres pacientes con hipopituitarismo, la excreción de catecol fué marcadamente subnormal.

La infusión de epinefrina aumentó las lecturas de catecol total por muy poco solamente, infusión de norepinefrina no se pudo descubrir en la orina por colorimetría. Simpatectomía unilateral toracolumbar fué seguida por una diminución transitoria de catecoles urinarios pero esto no fué aumentado más con una simpatectomía contralateral. Los catecoles del tejido simpático, obtenidos en la segunda operación y comparados con los tejidos en la primera, aparecieron reducidos 90 por ciento en dos pacientes examinados. Esto sugiere que luego de una simpatectomía parcial hay una sobredescarga compensatoria del tejido simpático restante. En pacientes urémicos, la excreción de los catecoles conjugados fué significativamente disminuida. Esto es consistente con el hallazgo regular y característico de catecoles elevados presumiblemente retenidos en la uremia renal.


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# The Response of the Renal Circulation in Man to Constant-Speed Infusions of *l*-Norepinephrine

*By* THEODORE N. PULLMAN, M.D., AND WILLIAM W. MCCLURE, M.D.

The effects of constant-speed intravenous infusions of *l*-norepinephrine in man have been studied with reference to the changes produced in the renal circulation. The responses to four rates of infusion were studied both qualitatively and quantitatively in each of nine normal men. As dosage was increased glomerular filtration rate changed little if at all, effective renal plasma flow diminished, and filtration fraction rose. Both afferent and efferent glomerular arteriolar resistances sharply increased, but the latter did so much more markedly than the former.

NOREPINEPHRINE, a naturally occurring pressor amine with potent vasoconstrictor properties, has recently been the subject of much study and investigation. This hormone has been shown to constrict the peripheral arterioles[1-4] both in cutaneous vessels and in skeletal muscle,[5] to increase the pressure in the pulmonary circuit[1] (although this is primarily due to an increase in pulmonary venous pressure rather than to a constriction of the pulmonary arterioles[4]), to diminish the cerebral blood flow,[6, 7] to reduce slightly the hepatic blood flow,[8] to dilate the coronary arteries,[9] and to produce splenic contraction.[9] It also causes a rise in peripheral venous pressure[4] and constricts the arterial segments of the terminal capillary loops in the nailfold.[10] Its pharmacodynamics has been thoroughly reviewed in recent publications.[11, 12]

Studies on the effects of norepinephrine upon the renal circulation have been far less extensive. Barnett and co-workers[13] showed that this hormone reduced renal blood flow in man. Six subjects were studied, each at a single dose of 20 to 30 micrograms per minute. Although all six men showed a reduction in renal blood flow, the experimental observations were confined to a single clearance period in each subject. In the dog, norepinephrine has been reported to diminish the renal blood flow[14] and also to produce no change in it.[15] Our own observations[16, 17] and those of Werkö and associates[18] support the assertion that norepinephrine is a renal vasoconstrictor in man. Both of these research groups have shown that the hormone increases renal resistance. However, in the latter investigation,[18] the segmental resistances were calculated by formulas[19] in which a value for the renal venous pressure enters into the computation. In the study of Werkö and his colleagues, this parameter was apparently not measured and an assumed value would have to have been used in the calculations. Since norepinephrine[4] as well as other vasoconstrictors[20] have been shown to alter venous pressure, the assignment of an assumed and constant value to the venous pressure seems invalid to us. At any rate, the detailed relation between dose and response was not the subject of Werkö's study.

On the glomerular filtration rate in man, norepinephrine has been reported to produce "small changes in both directions,"[18] slight falls,[13] and no change.[13, 21] In the dog, filtration rate has been reported to show no change,[15] or a depression.[14]

In view of these discrepancies, and because of the suggestion[1] that norepinephrine plays an important role in the pathogenesis of essential

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These experiments have been reported in part in a paper read by title before the Central Society for Clinical Research, Nov. 2, 1951.[16]

hypertension, it seemed advisable to us to attempt to ascertain definitively, both qualitatively and quantitatively, the renal hemodynamic effects of norepinephrine in man. Further impetus for physiologic quantitation in this regard stems from the clinical therapeutic use of norepinephrine in a variety of hypotensive conditions, such as surgical, hemorrhagic, and traumatic shock, after sympathectomy, after excision of pheochromocytomata, and after acute myocardial infarction.

We have attempted, therefore, to define the effects in man of constant speed *l*-norepinephrine infusions upon glomerular filtration rate, effective renal plasma flow, afferent glomerular arteriolar resistance, and efferent glomerular arteriolar resistance in normal man and to quantitate the dose-response relationships.

## Methods

### *Experimental Procedure*

The subjects were nine clinically normal young men. Glomerular filtration rate was measured by inulin clearance, and effective renal plasma flow by para-aminohippurate (PAH) clearance. Each subject was placed on a normal diet of constant and known composition a week before the experiment was to take place. All studies were made in the morning after a ten-hour fast. After a suitable priming injection, a solution of inulin and para-aminohippurate in 0.85 per cent saline was administered intravenously by a Bowman constant speed infusion pump at a rate calculated to produce an inulin concentration in serum of about 30 mg. per 100 ml. and a para-aminohippurate concentration of 1 to 2 mg. per 100 ml. Urine was collected through a multieyed catheter, and the bladder rinsed with distilled water or inflated with air at each emptying. In order further to minimize errors in urine collection, the studies were performed under water diuresis, each subject drinking 200 ml. of tap water every 20 minutes, starting two to three hours before the beginning of the experimental observations. Femoral arterial blood samples were collected at midperiod under oil by means of an indwelling Cournand needle. All blood was centrifuged and the serum separated with minimum possible delay.

After about 30 minutes (to allow for equilibration), a second slow intravenous infusion of 0.85 per cent saline was started in a different vein. The bladder was then emptied, and, after two control periods, a solution of 5 to 10 micrograms per milliliter of *l*-norepinephrine* in 0.85 per cent saline was substituted for the control saline. This solution was freshly made up just before use and was also administered by constant speed infusion pump. Four successive pairs of clearance periods were then performed, stepwise increments in rate of norepinephrine infusion being made at the end of each pair of periods. The dosage range studied varied from 2.0 micrograms per minute to 37.6 micrograms per minute. The period of administration at each dosage rate was approximately 20 minutes. Blood pressure was determined once a minute by sphygmomanometer.

An additional subject was studied in a somewhat different manner. After four control clearance periods (employing the same technics as outlined above), an intravenous infusion of *l*-norepinephrine was started and the rate of flow adjusted by a 4 cm. channel clamp. The rate was adjusted so as to maintain an approximately constant blood pressure of 210/110. The dose thus administered was calculated by a running count of the number of drops passing per minute through the calibrated Murphy drip.

### *Chemical Methods*

Inulin was determined in cadmium sulfate filtrates of serum and urine by the method of Roe.[22] Para-aminohippurate was determined in the same filtrates by the method of Smith and associates.[23] Hematocrits were determined on alternate blood specimens, with dried heparin as anticoagulant. Serum proteins† were determined by a modification of the Howe[24] precipitation and Kjeldahl digestion.

### *Calculations*

Inulin clearance was calculated in the conventional way as the product of the urine flow (milliliters per minute) and the concentration of inulin in urine (milligrams per 100 ml.) divided by the concentration in serum (milligrams per 100 ml.). All clearance values were corrected to a surface area of 1.73 square meters. Afferent and efferent arteriolar resistances were calculated according to the formulas of Lamport.[25, 26]

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* We are indebted to Dr. M. L. Tainter, of the Sterling-Winthrop Research Institute for a generous supply of *l*-norepinephrine (Levophed).

† We are indebted to the Billings Hospital Clinical Chemistry Laboratory under Dr. Richard L. Landau for the serum protein determinations.

‡ Subsequent to the completion of a major portion of this work, Gómez[19] presented a new method for calculating resistance in various segments of the renal vascular tree. While not intending to render judgment upon the relative merits and validity of the two derivations, we have retained the Lamport formulas instead of those of Gómez because the latter require that renal venous pressure either be known or

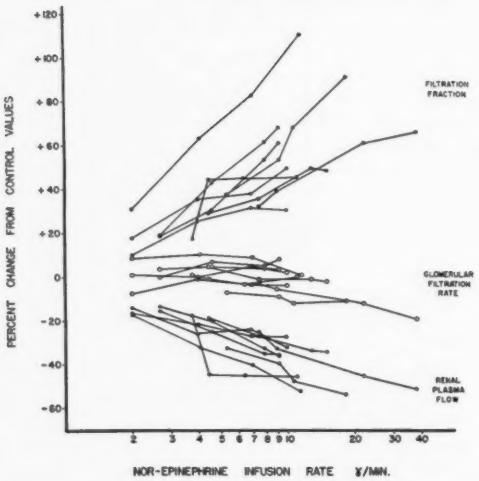


FIG. 1. Dose-response curves for glomerular filtration rate, effective renal plasma flow, and filtration fraction in nine normal men receiving graded constant-speed infusions of *l*-norepinephrine. Infusions were started at a low initial rate and then gradually increased in stepwise fashion. Each point represents the average of two clearance periods during which the *l*-norepinephrine infusion rate remained constant. The points representing the values thereby obtained in each subject are connected by straight lines.

## RESULTS

The dose-response curves for all nine subjects are illustrated in figure 1.

The glomerular filtration rate (GFR) changed little, if at all. One individual, who exhibited an unusually high tolerance to norepinephrine in terms of pressor response, showed a tendency towards diminution in glomerular filtration rate as higher infusion rates were achieved, but percentage-wise this change was not great.

The effective renal plasma flow (ERPF) showed a clear-cut and progressive decrease with increasing norepinephrine dose (fig. 1). One individual failed to exhibit further depression after the second increase in infusion rate.*

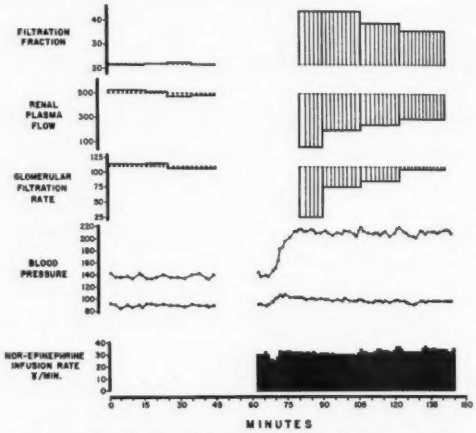


FIG. 2. Renal hemodynamic effects of an *l*-norepinephrine infusion when started abruptly at a relatively high rate of injection. The bars indicating filtration rate, plasma flow, and filtration fraction are erected from levels representing the mean values of these measurements during the control periods.

The filtration fraction (FF) rose as norepinephrine infusion rate was increased. As with the first two functions, percentile change was linearly related to the logarithm of the dose.

The results obtained on the subject who was started abruptly on a rapid rate of infusion of norepinephrine, rather than on a low rate with successive gradual increases, were quite different (fig. 2). When the norepinephrine infusion was started, both the glomerular filtration rate and the effective renal plasma flow fell sharply with a concomitant rise in filtra-

assigned an assumed value. Renal venous pressure was not measured in our experiments, and, since norepinephrine[4] as well as other vasoconstrictor substances[20] have been shown to alter venous pressure, we do not think it appropriate to assume an arbitrary "normal" value for this parameter in our subjects.

* The anomalous behavior of this subject is apparent in figures 1, 3, and 4. Since the experimentally determined effective renal plasma flow is employed in the calculation of the filtration fraction and the afferent and efferent arteriolar resistances, variations in the first of these parameters are reflected in the others. The experiment was repeated on this subject because his response was at variance with the other eight men. The data derived from the duplicate study were entirely in accord with those for the other subjects. However, since no experimental error could be found in the first run, either in the procedure itself or in the chemical laboratory, the data from this experiment have been retained and appear in the graphs in unaltered form.

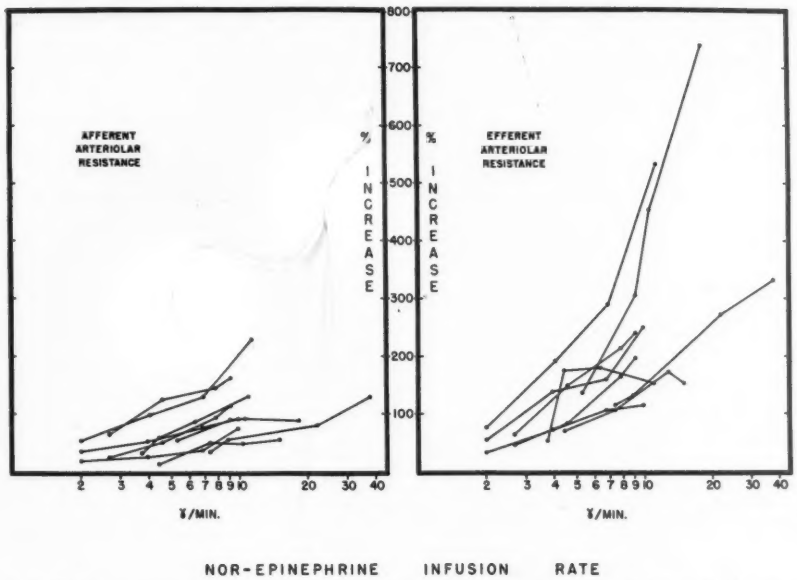


FIG. 3. Dose-response curves for afferent and efferent glomerular arteriolar resistance in nine normal men receiving graded constant-speed infusions of *l*-norepinephrine. Each point represents the average of two clearance periods during which the *l*-norepinephrine infusion rate remained constant. The points representing the values thereby obtained in each subject are connected by straight lines.

tion fraction. As the infusion continued, the glomerular filtration rate returned to control values, but although the effective renal plasma flow also rose, it remained well below the range observed before the norepinephrine infusion was begun.

The dose-response curves for the afferent and efferent glomerular arteriolar resistances are shown in figure 3. Although both these parameters rose with increasing dosages, the efferent resistances did so more sharply. In order to indicate the differential in responsiveness to norepinephrine of the afferent and efferent arterioles in each individual subject, the graphic method of figure 4 has been employed. In this figure, the difference between the percentile increments in efferent and afferent resistance are plotted for each subject against the corresponding dose. Thus, for any particular infusion rate, when the ordinate is positive and greater than zero, the percentage increment in efferent resistance exceeds that of the afferent. For any particular individual, when the dose-response curve has a positive slope, the percentage increase in efferent resistance is increasing more rapidly with increase in dosage than is that of the afferent resistance. As can be seen from figure 4, the response of the efferent arteriolar resistance to increasing doses of norepinephrine is clearly greater than that of the afferent resistance.

## DISCUSSION

It has seemed to us a refinement of dubious value to subject these data to exhaustive mathematical analysis, since simple inspection of the curves in figure 1 and figure 3 indicates a rough linearity between percentile change and the logarithm of infusion rate. This is in accord with Goldenberg's assumptions and observations that blood pressure bore a roughly rectangular hyperbolic relationship to norepinephrine infusion rate.[1]

There is general agreement that norepinephrine reduces renal blood flow in man while producing slight or inconstant changes in glomerular filtration.[16, 18, 13, 21] Recently, Moyer

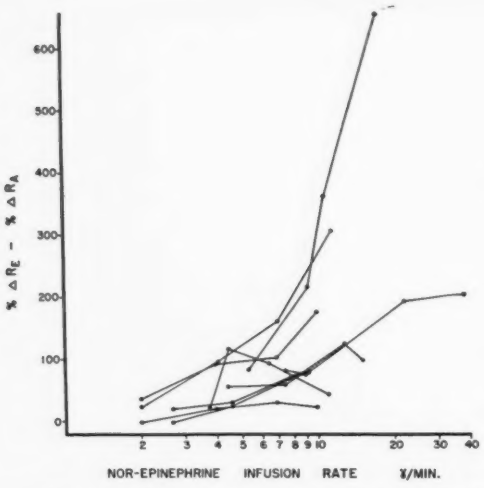


FIG. 4. Dose-response curves for the difference between the percentile increments in efferent and afferent glomerular arteriolar resistance in nine normal men receiving graded constant-speed infusions of *l*-norepinephrine. Each point represents the average of two clearance periods during which the *l*-norepinephrine infusion rate remained constant. The points representing the values thereby obtained in each subject are connected by straight lines. For interpretation of positivity of ordinate and slope, see text.

and Handley[14] have reported a decrease in glomerular filtration rate in dogs receiving intravenous norepinephrine. These dogs weighed from 10 to 20 Kg. and the doses employed were 10 micrograms and 30 micrograms per minute. A proportional dose for a 70 Kg. man would be much greater than those employed in establishing the dose-response curves herein reported. They may be considered more analogous to our experiment (fig. 2) in which a rapid rate of infusion of norepinephrine was started abruptly. If it is assumed that the rapidity with which a certain rate of norepinephrine administration is achieved influences the effect on glomerular filtration rate, some of the existing discrepancies in the available data are clarified.

The establishment of dose-response curves for normal human subjects makes possible investigations on the effects of various agents upon the responsiveness of the renal circulation to norepinephrine. Studies along these lines have been made in this laboratory with cortisone and desoxycorticosterone.[27]

## SUMMARY AND CONCLUSIONS

1. The effects of constant speed infusions of *l*-norepinephrine upon renal hemodynamics in normal men have been studied, and the responses of glomerular filtration rate, effective renal plasma flow, filtration fraction, afferent glomerular arteriolar resistance, and efferent glomerular arteriolar resistance have been established for varying rates of norepinephrine administration. Four rates of infusion were studied in each of nine subjects.

2. With increasing norepinephrine dose, the glomerular filtration rate remained essentially unchanged, the effective renal plasma flow decreased, the filtration fraction increased, and both afferent and efferent glomerular arteriolar resistance increased (the latter change exceeding the former). Percentile change in the parameters affected by norepinephrine showed an approximately linear relation to the logarithm of the rate at which the hormone was being administered.

## ACKNOWLEDGMENTS

The authors wish to acknowledge the encouragement and helpful criticism of Dr. Alf S. Alving, and the capable technical assistance of Miss Corinne Gordon, Miss Maxine Penn, Mr. Lowell Erickson, and Mrs. Dorothy Windhorst.

## SUMARIO ESPAÑOL

1. Los efectos de infusiones rapidas constantes de *l*-norepinefrina en la hemodinámica renal en hombres normales han sido estudiados y las repuestas en el promedio de filtración glomerular, circulación plasmática renal efectiva, fracción filtración, resistencia arteriolar glomerular aferente y resistencia arteriolar glomerular eferente han sido establecidas para variables velocidades de administración de norepinefrina. Cuatro velocidades de infusión fueron estudiadas en cada uno de nueve sujetos.

2. Con aumento en la dosis de norepinefrina, la filtración glomerular promedio permaneció esencialmente sin cambio, la circulación plasmática efectiva disminuyó, la fracción de filtración aumento, y ambas resistencias arteriolares glomerulares aferentes y eferentes aumentaron (la última más que la primera). Cambios en porcentaje en los parametros afectados por la norepinefrina demostraron una relación aproximadamente lineal al logaritmo

de la velocidad a la cual la hormona se administraba.

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## CLINICAL PROGRESS

# Nature and Treatment of Shock

*By* DICKINSON W. RICHARDS, M.D.

INTEREST in the practical problems of traumatic or wound shock in man, which was somewhat dormant after World War II, was reawakened by the military action in Korea, and has continued actively since. This has included both the analysis of various shock states, and their management; the study of problems of whole blood and plasma preservation and sterilization; the further development of plasma substitutes or plasma volume expanders; the use of arterial transfusions; the use of induced hypotension, especially in certain forms of surgery; and most recently, the use of induced hypothermia.

Experimental investigations in basic mechanisms of shock, on the other hand, have been in progress continuously since the end of World War II. In the medical field there has been recent interest in the question of infection in shock, and in the difficult problem of shock associated with myocardial infarction.

The present brief review will consider these subjects in turn.

### TRAUMATIC SHOCK

*Recent Reviews.* A number of review articles covering various aspects of shock have appeared recently. Among these may be mentioned those by Wilhelmi,[1] Davis,[2] Evans,[3] and Page[4]. Symposia have been published by the Army Medical Service Graduate School,[5] and the New York Academy of Sciences.[6]

An important contribution describing problems encountered in civilian disasters is that of Blocker and Blocker[7] on the Texas City explosion of 1949. Emphasis upon the predominant damage caused by flying glass fragments is one of the features of this report.

In a comprehensive monograph, "Observations on the General Effects of Injury in Man, with Special Reference to Wound Shock," Grant and Reeve[8] have analyzed their own large experience in World War II, and compared it with other published work. One of the chief concerns of these authors was to establish a satisfactory definition of the shock state. They have arrived at a somewhat complex description, consisting of six different circulatory patterns: (1) cold tachycardia: normal blood pressure, fast pulse, cold extremities, pale face; encountered only after injury, associated with moderate blood loss; (2) warm tachycardia: normal blood pressure, fast bounding pulse, warm extremities, well colored face; found with 70 per cent blood volume or in patients with very low hemoglobin; (3) hypertensive pattern: encountered soon after injury, and with but slight blood loss; (4) vasovagal pattern: low blood pressure, slow pulse, cold extremities, pale face; usually seen early, with emotional disturbance, occasionally terminally in patients dying of hemorrhage; (5) cold hypotension: low blood pressure, fast pulse, cold extremities, pale face; seen in advanced shock, with severe blood loss, also in advanced sepsis; (6) warm hypotension: low blood pressure, fast pulse rate, warm extremities; usually a transient state, with moderate blood loss, encountered in warm surroundings, often after operation.

So far as depth of shock is concerned, Grant and Reeve agree with most other authorities that except in cases of severe hemorrhage from local vascular injury, shock is best cor-

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related with the actual size of the injuries sustained.

*Experience with Battle Casualties in Korea.* Many problems arose due to the special circumstances of military action in Korea. These were under constant study; a special medical and surgical research unit, under the immediate direction of Major John O. Howard, was functioning during the last year of the war. Only preliminary reports of their investigations have as yet been made.[9]

With the widely scattered, entrenched positions that existed at the front, one of the difficulties was that of location and evacuation of wounded men. This sometimes resulted in long exposure after injury. Such cases later developed renal failure with anuria. The artificial kidney was used in a number of these cases, with some drop in blood nitrogen and plasma potassium, and at least temporary improvement.

If a wounded man is treated within three to four hours of his injury, he can be brought out of shock with sufficient blood in practically all instances except those of continuing rapid bleeding. Secondary shock may, however, develop later, especially during or after major corrective surgery.

Another genuine advance in treatment of the wounded has been the extension of reparative vascular surgery as an emergency measure.[10]

### *Practical Therapy*

The Committee on Surgery of the National Research Council has recently prepared a brochure entitled "Emergency Treatment in Major Disasters."[11] This is designed as a practical handbook, for use by the Federal Civil Defense Administration and similar agencies. It is presented in seven sections: I. Collection and Disposition of the Injured; II. Wounds; III. Wound Shock; IV. Burns; V. Fractures; VI. Acute Radiation Syndrome after Atomic Bombing; VII. Blood Transfusions. A few excerpts may be given from this excellent brief manual. It is noted that "burns, trauma, shock, and hysterical reactions are the major problems in the first hours after bombing." "In general, atomic casualties should be treated like any other injuries. Except with overwhelming dosage, symptoms of radiation injury appear late."

In the emergency treatment of the wounded, the principles are: "1. Arrest hemorrhage. 2. Check airway and respiration. 3. Treat shock immediately. 4. Diagnose extent of injury. 5. Relieve pain and anxiety. 6. Administer tetanus prophylaxis promptly. 7. Splint fractures. 8. Give first aid for eye injuries. 9. Evacuate first the wounded requiring surgery for resuscitation. These are: (a) intra-abdominal injuries, (b) extremity wounds requiring tourniquet, (c) intrathoracic injuries, (d) injuries with severe crush or laceration of muscle, (e) head and spinal cord injuries."

"Shock is expected after crushing injuries, traumatic amputations, major fractures, serious burns, large hemorrhages, chest and abdominal trauma. Severe extremity wounds are especially likely to cause rapidly developing shock. Except after massive hemorrhage, the fully developed picture of peripheral collapse associated with a fall of circulating blood volume may not appear for several hours. Shock may be recognized by: cool moist skin, pale or cyanotic lips, increasingly weak pulse, falling blood pressure, thirst and restlessness, collapsed peripheral veins, suppression of urine formation."

In treatment, "the most urgent duty of the physician is to restore blood volume," which will be reduced 15 to 20 per cent in mild cases, 40 per cent or more in severe cases. If the systolic blood pressure, after initial measures have been taken, remains below 80 mm. Hg, 1500 cc. to 2500 cc. of whole blood will usually be needed. Further details are given for treatment with plasma, plasma expanders, saline or glucose solutions, if whole blood is not available.

"If recovery from shock is not evident after adequate whole blood replacement (1500 cc. to 2500 cc.), the following possibilities arise: bleeding or plasma loss into injured areas is continuing, or blood loss is not responsible for the shock state."

#### *Blood, Plasma, Plasma Volume Expanders*

*Whole Blood.* All experience continues to support the position that whole blood transfusion is the best treatment for shock. Pro-

curement of blood by local agencies suffices for most civilian needs at present. For military needs the Red Cross program continues to be a basic necessity.

The primary efforts in research are being directed to (a) the preservation of blood for longer periods than the present three weeks provided by reduced temperature, with ACD solution (acid-citrate-dextrose) as an anticoagulant; and (b) sterilization of blood from hepatitis virus.

Deterioration of blood with time is progressive, even when kept at low temperatures. Blood 10 days to two weeks old may contain appreciable amounts of potassium and pigment in the plasma. With the multiple transfusions often given in severe shock, it is thought that hemoglobinemia and hyperpotassemia from this cause may be harmful, especially on renal function.

Of the many investigations in progress to prolong the useful life of whole blood, the mixture of red cells with glycerol followed by freezing at very low temperature, as developed in Great Britain by Mollison, Sloviter, and others,[12] is perhaps the most interesting.

*Plasma.* Pooled plasma, either as whole plasma or as dried plasma, which made so outstanding a contribution in the treatment of the injured in World War II, now carries so high an incidence of transmission of infectious hepatitis, that its present use by the Armed Forces has recently been prohibited by the Department of Defense. Sterilization of plasma is now the subject of extensive investigation. Ultraviolet irradiation has been shown to be ineffective. The chemical beta-propriolactone has shown some sterilizing action against the hepatitis virus, but its practical usefulness has yet to be demonstrated.

Human albumin solutions, produced by plasma fractionation, using cold ethanol followed by heating at 60 C., have been shown to be free of hepatitis virus, and this preparation is an excellent plasma expander. Other products of plasma fractionation are under study.

*Plasma Volume Expanders.* The onset of hostilities in Korea, and realization of the need for large volumes of fluid for blood volume replacement in the event of attack on civilian areas, have led to an extensive program of development of plasma substitutes or plasma volume expanders. An excellent recent review, with a large bibliography, is that of Gropper, Raisz, and Amspacher.[13]

The effort has been to obtain a material which on injection will sustain plasma volume to the extent of about half the volume infused, for a period of 8 to 12 hours; such material to be nontoxic, not stored in the body to an appreciable extent, either largely excreted or metabolized in the course of 48 to 72 hours.

Dextran. This material, a polymerized carbohydrate, is made by the action of the bacterial organism *Leuconostoc mesenteroides* on sucrose. The resulting polymer, of very high molecular weight, is then broken down by hydrolysis to an average molecular size of 75,000. Dextran was first suggested as a plasma expander in Germany,[13] later developed on a large scale in Sweden.[14]

Initial clinical studies in this country showed that while the dextran used was effective, there was a considerable incidence of toxic reactions of an anaphylactoid type.[13, 15, 16] It was later found that these products also produced skin reactions and specific agglutinins in normal subjects.[17, 18, 19] This reactivity was associated with the high molecular fractions. Reduction in molecular size of the dextran has largely eliminated these reactions.

In further studies, it has been shown that dextran is about 60 per cent excreted in 24 hours, and that the fraction retained is at least in part metabolized. No significant toxic effects on renal, hepatic or other systems have been demonstrated,[13] except for a recent finding of increased bleeding time following infusion. This is now being further investigated.

At present dextran of approved American manufacture has been released by the Food and Drug Administration, and passed by the Council on Pharmacy and Chemistry of the American Medical Association. It received extensive field trial in the Armed Forces.

Polyvinylpyrrolidone (PVP). This synthetic chemical, basically a polymerization of acetylene, was developed in Germany during World War II,[20] used extensively in the German army, and is still widely employed as a plasma

expander in Europe, particularly in France.[13] It is an effective expander and has essentially no immediate toxic effects. Its chief disadvantage is that it is not metabolized at all, and 20 to 40 per cent of the injected dose remains stored, especially in the cells of the reticuloendothelial system, for protracted periods, perhaps indefinitely. The possible consequences of such storage not being fully known, there has been a reluctance to accept this product for general use. The analogy that comes to mind is that of gum acacia, which was shown in some instances with large doses, to produce liver enlargement due to deposited acacia. There has been no evidence to date of any such change produced by PVP.

The gelatins. During World War II a purified gelatin, lightly degraded or hydrolyzed, was found to be an adequate plasma expander. The chief disadvantage of this product was that it was viscous or semi-solid at room temperature and required warming before administration. In recent years there has been a considerable effort devoted to producing a gelatin which would remain in the circulation long enough to serve as a plasma expander and yet remain fluid down to freezing temperatures. Chief among these products are oxypolygelatin and "modified fluid gelatin."[13] Developmental work on these products is still in progress.

Other products, still in an experimental stage, are mentioned in the review of Gropper, Raisz, and Amspacher.[13]

*Saline and Alkaline Salt Solutions*

The question is still raised from time to time, whether these solutions will not be adequate in treatment of shock, and can replace plasma, plasma expanders, or even blood. The majority of opinion at the end of World War II was that, while added amounts of saline (sodium chloride or sodium lactate) might be useful early in the treatment of burns, these solutions were not generally adequate for treatment of severe injury with shock.[21] Saline can sustain the circulation for short periods while blood is being obtained. The prime objective in the use of salt or glucose solutions in conditions associated with shock might be said to be the maintenance of urine volume, rather than the restoration of blood volume.

*Hypotension as a Procedure in Surgery.* Hypotensive agents, such as the hexamethonium compounds, have been used to reduce blood pressure and aid in the control of bleeding, in extensive surgical operations. This has received much attention recently.[40, 41, 42] Systolic pressure is reduced to 50 mm. or 70 mm. Hg, restored again before the operation is over, by Neo-Synephrine infusion. High spinal anesthesia has also been used.[43] These procedures have to be used with great care; overprolonged hypotension has resulted in blindness, hemiplegia, coronary occlusion, and cardiac arrest.

*Arterial Infusion.* This technic, originally suggested by Seeley,[44] and developed by Kohlstaedt and Page,[45] has a place, somewhat more limited than at first anticipated, in the rapid restoration of the circulation in cases of extreme shock. Blood is infused into a peripheral artery, usually in amounts from 250 to 500 cc., at inflow pressures around 100 to 120 mm. Hg, sometimes rapidly (75 to 100 cc. per min.), sometimes slowly (250 cc. in 30 minutes). Results in both acute surgical or operative emergencies, and in medical shock, such as that with myocardial infarction, have been quite variable.[45, 46, 47] The general purpose is to restore the circulation of vital organs, such as heart and brain, rapidly, hoping that the myocardium itself will then take over.

*Hypothermia.* While induced hypothermia has been tried in various clinical conditions for a number of years, its systematic use in surgery is quite recent. It has been developed particularly in France.[59, 60, 61] The essential features include: (1) The use of a combination of pharmacologic agents to provide sedation, vasodilatation, and "stabilization" of the circulation. The phenothiazine derivatives Phenergan and Largactil are among key agents used. (2) Body cooling to maintain central body temperature around 30 to 32 C. The surgery is performed at this temperature. (3) Very gradual rewarming over a period of many hours. The procedure is difficult and

complicated; the details cannot be included in this review.

These same principles have been applied in the treatment of shock. Here the drugs used often result in a hypothermia, and little additional cooling is needed. Blood and other fluid is of course given as required. Extensive experience has now been obtained in the French military theatre in Indo-China.[61] Injured men are maintained for two and three days in the hypothermic state, semiconscious or unconscious, are transported from the front to hospitals, receive the necessary surgery, and are then returned slowly to normal temperature. Although the full value of such treatment is still under study, it is certainly a signicant and interesting development.

### *Fundamental Mechanisms of Shock*

In a clinical review, no adequate account can be given of the many and complex studies that have been in progress in recent years, on various fundamental mechanisms related to the shock state. A few of the notable contributions will be outlined briefly. Summaries of current work are given by Wilhelmi,[1] Page,[4] and in the Macy monographs on Shock and Circulatory Homeostasis.[22, 23]

### *Irreversible Shock*

To the experimental physiologist and the clinician alike, the greatest interest has centered around the phenomena of "irreversible shock," the condition developing after a more or less protracted period in moderate to severe shock, when the organism no longer responds to fluid replacement or other measures, and steadily fails and dies in a hypotensive state. In the experimental animal, irreversible shock can be produced by a variety of techniques: such as graded hemorrhage with protracted maintenance of hypotension, crushing or pounding a limb, or revolving the animal a certain number of times in the "Noble-Collip" drum.

*Vasomotor Factors.* One of the significant advances in physiology in recent years has been the elucidation of the relative roles played by adrenaline and noradrenaline in the animal body, through the work of von Euler and his collaborators,[24] Goldenberg and coworkers,[25] and others: noradrenaline the actual chemical transmitter liberated at the sympathetic or adrenergic nerve endings, constricting blood vessels without altering cardiac output; adrenaline, liberated only by the chromaffin cells of the adrenal medulla, raising blood pressure only secondarily through increased cardiac output, having actually an over-all vasodilator effect in physiologic concentrations, and with many metabolic and hormonal actions. Von Euler has recently postulated that noradrenaline may play a further role in relieving shock, by narrowing the venous vascular bed where pooling has taken place.[24]

There is evidence that the action of noradrenaline may be potentiated by adrenocortical steroids.[26] Clinical results with the use of this and related agents will be referred to later.

In 1944, Chambers and Zweifach,[27] studying the action of the smaller blood vessels in the mesoappendix of the rat, found changes in the appearance and action of these vessels when perfused with blood from animals in severe shock. The actual form of vasomotion used was the increase or decrease in the vasoconstrictor action of epinephrine. On the basis of this finding, Shorr and Zweifach and their associates[28] have since carried out extensive studies. Briefly summarized, it has been shown that in several forms of experimentally produced shock, there occurs at first a hyper-reactive, vasoconstrictor state, caused by the formation in the (anoxic) kidney, and appearance in the blood, of a vasoexcitor principle, termed VEM. At this time, a vasodilator principle, VDM, is being formed by the liver, but also inactivated by the liver. Later, during the stage of profound hypotensive and irreversible shock, the (anoxic) liver no longer inactivates VDM, which then appears in the blood in increasing amounts, and is considered by these investigators to be largely responsible for the irreversible hypotensive state.

VDM has been shown to be the iron-containing protein ferritin. It is activated, as the sulfhydryl form, by anaerobic liver tissue; it is inactivated, as the disulfide form, by

aerobic liver tissue. The chemical nature of VEM has not been worked out; it is activated by anaerobic kidney tissue, inactivated by aerobic. One of the interesting recent developments in these studies has been the correlation between VDM and the resistance developed in rats when subjected repeatedly to the Noble-Collip drum. As is well known, by repeated sublethal rotations in this apparatus, rats become relatively resistant and can tolerate "drummings" lethal to unpracticed rats. Shorr and Zweifach[23, 28] have found that in resistant rats there is a corresponding decrease in blood VDM, and increase in the ability of liver slices from these rats to inactivate VDM.

Shorr and Zweifach believe that this mechanism plays an important role in the cause of irreversible shock. Question has been raised in regard to their findings because all the results are based upon observations of a particular reaction in one specialized tissue. Recently Fine[6] has given large doses of activated ferritin to a hepatectomized, renalectomized dog and no fall in blood pressure or other circulatory change occurred. Shorr and Zweifach[6] claim that the VDM, VEM mechanism concerns the smaller vessels only, and should not be expected of itself to cause hypotension.

Physiologists have been much interested recently in certain vasodilator agents, especially Dibenamine, which, while producing a profound hypotensive state, still permits severe hemorrhage to take place without the development of irreversible shock.[4, 22, 23] It suggests that some of the body's reflex or "compensatory" vasoconstrictor reactions may actually be harmful. The relation of Dibenamine hypotension to that recognized in the vasovagal reaction of clinical syncope, or fainting, is also of interest, syncope being a reaction in which arterial blood pressure falls with but little alteration either in blood volume, cardiac output, or the pressure of venous return flow to the heart,[29] apparently a direct collapse of arteriolar tone. These experimental studies are somewhat complex, and further clarification is needed. The use of vasodilator agents in clinical surgery will be referred to later.

*Factor of Infection.* Clinically, while irreversible shock may be precipitated immediately after massive injury, it is more likely to come on progressively, when after initial resuscitation, the patient suffers some additional strain such as operation, or infection. In this condition, massive replacement with blood, bringing blood volume, and venous pressure also, to or even well above normal values, is associated with less and less response by the heart and arterial pressure; the latter finally fails progressively, the patient passes into coma, and expires. Among nontraumatic medical conditions, a not dissimilar picture may be seen in severe septic states, except that here the blood volume may be normal throughout.[30]

"Toxic" substances of infectious origin have long been searched for, as causative agents in both medical and surgical shock. During the war, Aub and his colleagues,[31] studying the shock that developed in dogs with gastrocnemius muscles tied off, found that the hypotensive collapse occurring after release of the ligatures was due to a toxin elaborated by clostridial organisms in the muscles during the period of ligation. Fine and his associates made similar observations at about the same time. Frank, Seligman, and Fine[32] also demonstrated that irreversible hemorrhagic shock in dogs could be prevented either by cutting the liver out of the circulation, or by perfusing the liver with oxygenated blood from another animal, while the first dog was bled. Coming back to this problem again, Fine and his associates have recently made further observations on the infectious factor in shock.[6, 22, 23, 33] Dogs normally harbor intestinal bacteria in their livers, in a large percentage of animals, particularly Clostridia. During shock these organisms grow rapidly. If the animals have been pretreated with Aureomycin, orally or by portal injection, or with Neomycin orally, then they are able to survive the standard lethal bleeding procedure, in most instances. This is evidence suggesting that infection plays an important role in the irreversibility of acute shock in

dogs. The nature of the substance or bacterial agent causing the irreversible state has not been identified. It has been shown, for example, that the number of clostridial organisms in the dogs' livers is the same in treated and in control groups. This work is still in progress.

*Metabolic Factors.* Studies during World War II[34] showed that in severe progressing traumatic shock, the tissues generally appear to be much more severely affected than would be expected from the depression of the circulation as a whole. Cardiac output may be decreased by about one-half, a situation frequently encountered in ambulatory cardiac patients, and yet there develops in the shock state a profound acidosis, presumably on the basis of tissue anoxia. It would appear that blood circulation through capillaries may be more seriously deranged than the total blood flow.

Investigation of the metabolism in shock in experimental animals, also going back to the early years of World War II, has indicated that following the early responses to injury, such as hyperglycemia and increased protein catabolism, there occur progressing evidences of tissue anoxia, anaerobic glycolysis, increased blood lactate and pyruvate, increased blood amino acids, etc. It is now generally agreed that while the adrenal cortex participates in these changes, its activity is in no way causative in traumatic shock.[6, 35]

The metabolism of individual organs in shock has been under study for many years. The depression of renal function, with marked decrease in renal blood flow progressing, if unchecked, to ultimate renal failure in the syndrome of lower nephron nephrosis, was fully worked out in World War II.[36, 37, 38] The depression of hepatic function appears also to proceed largely from progressive anoxia, with recovery when the circulation is restored.[23]

In classic traumatic shock, the chief difficulty suffered by the heart is insufficient return of blood to the right auricle. In irreversible shock in dogs, Wiggers[39] has produced evidence, over a period of some years, that there is a true failure of the myocardium. In his experimental animals, during the state of irreversible shock, venous return is adequate, while cardiac output remains diminished. Heart size may be increased. Whether this occurs in human irreversible shock is not known. Sharpey-Schafer suspects that there may be a cardiac element in syncope, or late in hemorrhagic shock.[22]

The shock occurring in myocardial infarction is a different entity. This will be discussed further presently.

## Medical Shock

### *Overwhelming Infection*

Vigorous antibiotic therapy is the mainstay in overwhelming bacterial infection with shock developing in the presence of normal blood volume. Whole blood transfusions are often of temporary aid. The use of cortisone or corticotropin has apparently been effective in some cases of Waterhouse-Friderichsen syndrome.[48-52]

### *Shock in Myocardial Infarction*

Sustained shock in myocardial infarction is attended by very high mortality, usually reported as about 80 per cent, but varying somewhat with the definition of "shock." Transitory fall of blood pressure is of course one of the common events in acute myocardial infarction of moderate or even mild degree. When, however, at any time in the course of an acute infarction, the blood pressure and pulse pressure drop to shock levels, remain there for several hours, and, even more important, are associated with the clinical evidences of the shock state, the clinical picture is easily recognized. Granting that the primary event is myocardial failure, and that there frequently are associated signs of congestive failure as well—pulmonary edema, and elevated venous pressure—nonetheless there are present also all the evidences of true peripheral circulatory failure,[56] with all the consequences of the progressing anoxia of shock.

The usual therapy for acute myocardial infarction is administered: morphine, oxygen (by positive pressure mask if there is frank pulmonary edema), intravenous digitalis.

Ethyl alcohol inhalation has been recommended for the pulmonary edema.[53]

The basic controversial question is whether the above are all that should be done, or whether the "tired horse" should be "whipped," that is, blood pressure elevated by drugs, and blood flow forced by infusion or transfusion, in the hope that the temporary dynamic improvement so achieved can thereafter be sustained.

Most recent writers appear to favor the use of a vasopressor agent to maintain arterial pressure for 12 to 48 hours: such as Paredrine, Neo-Synephrine, or norepinephrine.[54, 55] Many cases, of course, fail to respond adequately, some do not respond at all.

Opinion is more divided on the use of infusions or transfusions.[46, 47, 55, 58] This has been a controversial question for a number of years. Cochran, Wallace, and Griffith[57] are among those who believe they are not beneficial. Gootnick and Knox[55] advocate intravenous fluid, plasma, or blood, unless there is frank pulmonary edema, in amounts up to 1500 cc. over periods of 7 to 48 hours. Intra-arterial transfusions have been reported by Silber and co-workers[46] and Berman and Akman.[47] It is difficult to evaluate these various results; mortality usually appears to be less with the procedures used, but remains 50 per cent or higher.

Intravenous cholinesterase and intravenous and intramuscular cortisone gave results "suggesting a beneficial role" in preliminary studies by Cochran, Wallace, and Griffith.[57]

Physiologic theory will hardly be able to give the answers on these therapeutic questions; they will have to await the accumulation of much careful clinical trial.

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# ABSTRACTS



## AVITAMINOSIS, NUTRITION AND HEART

**Walters, J. H.: Hyperpiesis in Cardiovascular Beriberi.** Quart. J. Med. **22:** 195 (April), 1953.

The author observed an outbreak of acute cardiovascular beriberi among men working in the pearl-fishing fleet in the Persian Gulf in the summer of 1951. Eight cases from this series and one additional case in which the disease arose under similar circumstances are reported. All the cases presented a similar clinical picture. Symptoms in these patients developed within a few weeks of one another about three months after the fleet had put to sea. These patients showed gross anasarca, myocardial damage, arterial hypertension and minimal or no signs of peripheral neuritis. In the majority of patients epigastric pain accompanied the onset of edema and apparently was due to distention of the liver capsule. The edema was generalized and was not produced by hypoproteinemia nor was it necessarily associated with heart failure. In six patients myocardial damage was evidenced by symptoms, physical signs, x-ray evidence of cardiac enlargement and abnormal electrocardiograms. A blood pressure greater than 150/90 mm. Hg was found initially in four patients and a further rise appeared in two with treatment. Four of the other five patients developed significant hypertension within four days after treatment with Aneurin was started. The one patient who did not show hypertension died within 24 hours after treatment. In one patient hypertension led directly to death; in another it resulted in an attack of left ventricular failure, and in a third produced cerebral symptoms. The author discusses the possible mechanism of the appearance of hypertension in terms of renal anoxia as a result of an edema raising tension within the renal capsule which obstructs blood flow within the renal vessels. Aneuria may enhance this renal anoxia by causing acute arteriolar constriction before the edema had been dispersed. The cardiac failure in beriberi is of the high output type and its basic mechanism combines general arteriolar dilatation and myocardial weakness. Treatment with Aneurin leads rapidly to arteriolar constriction which should reduce the venous return to the heart. It also causes a return of fluid into the intravascular compartment. This latter effect may increase the circulating blood volume and in the presence of diminished renal excretion produce a hypertensive effect. With severe myocardial damage Aneurin, therefore, may have a deleterious effect producing left ventricular failure. Although the ultimate prognosis in cardiovascular beriberi has been considered to be a complete recovery if the patient survives the early phases of acute cardiac failure, one case in this series showed that irreparable myocardial damage may persist despite recovery from the acute stage of cardiac failure.

SAGALL

**Benchimol, A. B., and Schlesinger, P.: Beriberi Heart Disease.** Am. Heart J. **46:** 245 (Aug.), 1953.

The authors summarize their experiences with 22 patients with beriberi heart disease observed during a period of three years in Rio de Janeiro, Brazil. In most patients, beriberi was the only etiologic factor, but there were some instances of other associated cardiac conditions, notwithstanding the fact that the vitamin deficiency was the main cause in all cases. Chronic alcoholism was the major etiologic factor. All patients but one were between 30 and 40 years of age; the exception was 52 years old. All were men. The earliest and most frequent clinical manifestation was dependent edema. Clinical or

roentgenologic signs of pulmonary congestion were observed in 19 cases. Blood pressure variations were observed, particularly a transient hypertension during the course of heart failure. A transient bradycardia usually appeared at the onset of clinical improvement. Polyneuritis was found in 20 patients. Electrocardiographic signs of left ventricular hypertrophy occurred in eight patients, four of whom showed associated T-wave changes. One patient, aged 33 years, had a complete left bundle branch block. In three patients, the T-wave inversion became more marked as the patient improved. Regular sinus rhythm occurred in all but one case in whom ventricular premature beats were present, but this was attributed to digitalis toxicity. Most of the patients showed cardiac enlargement by x-ray. Nine patients with enlarged hearts on admission had normal sized hearts on discharge. Six patients died, all of heart failure. Necropsy findings on five revealed changes consistent with thiamine deficiency, including interstitial edema, dissociation of the myocardial fibers, and myocardial fibrosis.

RINZLER

## BACTERIAL ENDOCARDITIS

**Keefer, C. S.: Present-Day Treatment of Subacute Bacterial Endocarditis.** J. A. M. A. **152:** 1397 (Aug. 8), 1953.

Within recent years it has been found that in many cases bacterial endocarditis can be treated successfully. It has been shown that at least 90 per cent of all strains of *Streptococcus viridans* are inhibited by concentrations of penicillin of 0.01 to 1 unit per milliliter. If the organism is resistant in one or more units of penicillin per milliliter then the results of treatment with penicillin alone are not satisfactory. Such cases require combined antibiotic therapy. For combined therapy resistant organisms should be tested for their sensitivity in vitro. It has been suggested that the minimum daily dose of penicillin should be at least 2,000,000 units and that treatment should be continued for a minimum period of four to six weeks. With larger doses of penicillin combined with streptomycin, and large doses of penicillin alone, for short-term treatment, favorable results have been found, but the patients should be watched very carefully for signs of relapse or recurrence. Over-all results of present treatment can be summed up as follows: (1) Sixty to 70 per cent of the patients recover and remain well and asymptomatic for a period of years. (2) Some patients recover from signs of infection and die later of heart failure, uremia, or cerebral embolism. (3) Some patients die during treatment (this group comprises about 10 to 20 per cent of all cases). (4) Some recover from an initial infection only to have reinfection occur at a later date. This group is very small (about 2 per cent). To assure complete victory over subacute bacterial endocarditis, physicians must first achieve the prevention of rheumatic heart disease, the complete prevention of infection, and the prevention of congenital heart disease. These goals can be reached only through the pursuit and accumulation of scientific knowledge.

KITCHELL

**Garrido Lecca, G., and Tola, A.: Subacute Bacterial Endocarditis Treated with Chloramphenicol and Oxytetracycline.** J. A. M. A. **152:** 913 (July 4), 1953.

In this case of subacute bacterial endocarditis caused by streptococcus viridans, penicillin and Aureomycin had been used without effect. Sensitivity tests indicated the microorganism was sensitive to chloramphenicol and oxytetracycline. It was resistant to penicillin, Aureomycin and streptomycin. After adequate treatment with chloramphenicol and oxytetracycline complete recovery resulted. Although some evidence exists of the antagonism between certain antibiotics an in vitro test should always be done in the treatment of infections until a more complete knowledge of the mechanism of action of these drugs is known.

KITCHELL

## BLOOD COAGULATION

**Wessler, S.: Studies in Intravascular Coagulation. II. A Comparison of the Effect of Dicumarol and Heparin on Clot Formation in Isolated Venous Segments.** J. Clin. Investigation **32:** 650 (July), 1953.

The effects of two anticoagulants were studied by using a technic which produces an isolated blood-filled venous segment in a dog. It was previously found that a fibrin clot developed before the disappearance of demonstrable amounts of prothrombin. Since Dicumarol is employed to inhibit or retard intravascular coagulation in man, a study was made to ascertain whether induced hypoprothrombinemia was associated with retarded fibrin deposition under these experimental conditions.

In this study, severe Dicumarol-induced hypoprothrombinemia did not markedly retard the fibrin deposition of an isolated venous segment unless sufficient Dicumarol had been administered to greatly prolong the clotting time of the blood. On the other hand, heparin in therapeutic doses did have a significant retarding effect on intravascular coagulation. These observations do not necessarily suggest that heparin is a more suitable anticoagulant than Dicumarol in clinical practice, since the failure to demonstrate clot inhibition with Dicumarol may be inherent in the method employed. The significance of the study reported herein lies in the observation that Dicumarol and similar substances which depress that part of the coagulation mechanism concerned with the conversion of prothrombin, may not provide as optimal an anticoagulant property as

heparin-like compounds which block the deposition of fibrin through other mechanisms.

WAIFE

**Lewis, R. B., and Moen, P. W.: Further Investigations on the Use of Heparin in the Treatment of Experimental Frostbite.** Surg., Gynec. & Obst. **97:** 59 (July), 1953.

The authors investigated the possible therapeutic role of heparin in experimental frostbite through a study of the incidence or extent of gangrene in frozen rabbit legs. During the period of observation the blood coagulation time was continuously increased to 30 minutes or longer. The injury was produced by exposing a hind leg to cold alcohol at either −12 or −15 C. for 30 minutes.

Comparison of the results in heparinized and control animals revealed that the incidence and degree of gangrene were not less in the former group. At the same time the death rate in the heparin-treated rabbits was significantly greater.

ABRAMSON

**Rose, O. A., Ott, R. H., Jr., and Rubin, S.: Hemopericardium with Tamponade during Anticoagulant Therapy of Myocardial Infarct.** J. A. M. A. **152:** 1221 (July 25), 1953.

An instance is reported of hemopericardium with cardiac tamponade in a 48 year old man who was being treated with anticoagulant therapy for acute myocardial infarction. Pericardiotomy was a life-saving procedure. The possibility of such a complication during anticoagulant therapy should be kept in mind.

KITCHELL

**Owen, C. A., and Hurn, M. M.: Changes in Blood Coagulation Factors during the First Week of Life.** J. Pediat. **42:** 424 (April), 1953.

Various factors concerned with the clotting of blood were studied in normal, full-term infants during their first week of life. During the period when so-called prothrombin times were lengthened, infant blood was deficient in both prothrombin and the stable factor, but not in the labile factor.

When an analogue of vitamin K was administered at birth, the infants' prothrombin times tended to remain normal, the concentration of prothrombin was still diminished, the concentration of the stable factor approached adult values and the amount of labile factor continued to be normal or was more than adult values. Variations in the blood clotting of infants during the first week of life as measured by the Quick test, appeared to parallel the concentration of the stable factor. This is in agreement with the concept that the Quick test is primarily an index of the accessory conversion factors and not of prothrombin activity.

BERNSTEIN

## CONGENITAL ANOMALIES

**Limón Lason, R., Eclavissat, M., Puech, P., de la Cruz, M. V., Rubio, V., Bouchard, F. and Soni, J.: Cardiac Catheterization: V. Interatrial Septal Defect.** Arch. Inst. Cardiol. Mexico, **23:** 279 (June 30), 1953.

Fifty cases of atrial septal defect were studied from a clinical, roentgenologic, and hemodynamic point of view. Experiments on fresh human hearts confirmed that the right atrium is more extensible than the left and may hold a greater amount of fluid under a lower pressure.

The cases are classified in three groups: (a) left-to-right shunt; (b) two-way shunt; and (c) right-to-left shunt.

First degree A-V block was common while complete A-V block was rare (one case). Right bundle branch block was constant; it was complete in three cases and incomplete in the others.

*Uncomplicated Defect.* Right ventricular and pulmonary pressures were normal or moderately elevated and usually between 35 and 60 mm. Hg. A smaller group had pressures between 60 and 80. In this group, no relationship was found between type of shunt and intracardiac pressures. On the other hand, patients with a two-way shunt or pulmonary hypertension frequently had palpitation, exertional dyspnea, and a loud systolic murmur. A diastolic murmur or an extremely loud pulmonary second sound were found in patients with elevated pulmonary pressures.

*Lutembacher Syndrome.* This clinical picture is less frequent than previously thought (6 cases out of 50). While the hemodynamic changes were similar to those of the other cases, the clinical, electrocardiographic, and roentgenologic pictures were modified (auscultatory evidence of mitral stenosis, larger heart, alterations of the P wave, qR complexes in $V_1$).

*Pulmonary Hypertension.* This is a possible complication of the atrial defect. There usually is a right-to-left shunt. The study of samples of pulmonary venous blood permits evaluation of the shunt and exclusion of structural pulmonary changes. The clinical picture (cyanosis, possible clubbing, possible systolic thrill over pulmonic area); the roentgenologic features (evidence of right ventricular hypertrophy, of slight left ventricular dilatation, and of dilatation of the pulmonary artery which may reach the stage of aneurysm); and the electrocardiogram (evidence of ischemia in $V_1 - V_2$), are different from those of the other groups.

LUISADA

**Lukas, D. S., Dotter, C. T., and Steinberg, I: Agenesis of the Lung and Patent Ductus Arteriosus with Reversal of Flow. Report of a Case.** New England J. Med. **249:** 107 (July 16), 1953.

The case of a man aged 22 years with agenesis of the left lung and a patent ductus arteriosus i

reported. There was clubbing and cyanosis of the toes, but not the fingers. This observation led to a clinical diagnosis of patent ductus arteriosus with pulmonary hypertension and reversal of ductus flow. The diagnosis was established by angiocardiography, bronchography and cardiac catheterization. The pulmonary arterial pressure was 113/70. There was evidence of shunting of oxygenated blood into the pulmonary artery. Angiocardiography disclosed evidence of both left-to-right and right-to-left shunting through the ductus. The oxyhemoglobin saturation in the right brachial artery was 94.1 per cent whereas that in the right femoral artery was 84.1 per cent. Surgical intervention was decided against in view of the reversal of flow through the ductus and the fact that a short, thick ductus was considered present.

ROSENBAUM

**Kent, J. V.: The Development of Rib Notching After Surgical Intervention in Congenital Heart Disease.** Brit. J. Radiol. **26**: 346 (July), 1953.

The author discusses the various disorders besides coarctation of the aorta in which notching of the ribs is present and then adds a new condition. This type of change is noted in hypertension, aortic and mitral valvular lesions, neurofibromata of the intercostal nerves and in tuberose sclerosis. It may also result from the pressure of dilated tortuous intercostal veins associated with a long standing obstruction of the superior vena cava.

The author's two cases developed notching of the ribs after surgical treatment of congenital heart disease. In one a left-sided thoracotomy was performed and subsequently the notching was noted on the left side only. In both instances the left subclavian artery was divided, thus removing the main blood supply to the arm. It was concluded that the erosions developed as a result of the participation by the intercostal arteries in the collateral circulation to the upper extremity.

ABRAMSON

## PATHOLOGIC PHYSIOLOGY

**Lequime, J., Denolin, H., Courtoy, P., and Kenis, J.: The Circulatory Dynamics in the Course of Mitral Stenosis.** Acta Cardiol. **8**: 353 (Fasc. 4), 1953.

The authors report on hemodynamics in 23 cases of mitral stenosis with reference to operability. In a first group of patients with no or negligible symptoms the findings were either normal or insignificantly altered. In a second group, corresponding to groups III and IV of the American nomenclature, the following alterations of circulatory functions were present: The cardiac output at rest was often but not invariably reduced. When exercise of sufficient duration to reach a steady state was performed, cardiac output proved insufficient to meet the augmentation of metabolic needs. Pulmonary arterial pressures and capillary pressures were high at rest and increased considerably under stress. The pressure gradient, however, may remain normal; its increase indicates functional or anatomic alterations of pulmonary circulation. The total pulmonary resistance was high and its increase was dependent on the degree of mitral stenosis and the alterations of the pulmonary vascular tree. The cause of the latter abnormality is obscure. The contour of the capillary pressure curve gives useful information particularly as to the presence of mitral regurgitation. In the latter condition there is an enlarged auricular wave which increases further on exercise. An estimation of the mitral area is justified, but an attempt to classify patients according to such calculations is not warranted, since clinical signs and symptoms depend also on the degree of pulmonary vascular changes which vary from patient to patient. The ratio of oxygen consumed per liter of ventilation decreases during exercise, regardless of the presence or absence of pulmonary congestion. This is apparently due to some central regulatory mechanism acting upon the respiration consequent to the maladaptation of cardiac output to oxygen consumption.

The authors recommend an accurate study of circulatory dynamics in all cases of mitral stenosis since only on the basis of such an analysis can the indication for commissurotomy be established and the results of commissurotomy anticipated.

PICK

**Epps, R. G., and Adler, R. H.: Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis.** Brit. Heart J. **15**: 298 (July), 1953.

Mean left atrial pressures and wedge pressures of the pulmonary artery were found equal in seven patients with rheumatic mitral valve disease. Wedge pressure tracings showed waves similar in form to those recorded directly from the left atrium. This confirmed the view that true wedge pressure tracings should have a venous configuration and that the waves recorded are transmitted from the left atrium.

Pulsations of the left atrium were recorded by means of a needle introduced into the left atrium through the medial wall of the left main bronchus. Wedge pressures were recorded immediately afterwards through a catheter which blocked a peripheral branch of the pulmonary artery.

LUISADA

**Epps, R. G., and Adler, R.: Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis.** Brit. Heart J. **15**: 298 (July), 1953.

A technique is described for measuring in rapid succession the pulmonary wedge pressure (pulmonary capillary venous pressure) and that of the left atrium. The left atrial pressure is measured by a needle passed through a bronchoscope which

pierces a point 1 to 5 cm. distal to the carina in the medial wall of the left main bronchus to enter the left atrial cavity.

Individuals were selected with sinus rhythm, auricular fibrillation, low and high pulmonary arteriolar pressure and with pure mitral regurgitation (one). In each instance, the mean pressures in the left atrium and in the blocked peripheral pulmonary artery were equal.

SOLOFF

**Bruce, R. A., and Rodgers, D. L.: Quantitative Effects of Medical and Surgical Treatment of Mitral Stenosis on Exercise Tolerance.** Am. J. Med. **15**: 35 (July), 1953.

The authors present the results of quantitative exercise tolerance tests in 20 patients with mitral stenosis who were studied on several occasions, both preoperatively and from 3 to 12 months postoperatively. In most instances there was demonstrable evidence of disability or impaired exercise tolerance when the patients were evaluated initially. Preoperative medical preparation resulted in improvement in 18 of the 20 patients. Although 70 per cent of the patients were clinically improved postoperatively, the improvement was delayed in about one-half. The majority eventually demonstrated significant increments in exercise tolerance. The importance of converting auricular fibrillation to normal sinus rhythm with quinidine therapy was demonstrated with respect to increased exercise tolerance postoperatively. Continued postoperative follow-up tests revealed deterioration of functional capacity in 7 of 20 patients studied from three to nine months after operation. The common factor apparent in all in this group was attributed to heart failure resulting from one or more variables. Exercise tolerance tests are an important adjunct to the clinical evaluation of patients with mitral stenosis in determining disability, minimal reserve for surgery, separating the effects of medical and surgical treatment and revealing postoperative complications, such as heart failure, which may not be appreciated by clinical examination.

HARRIS

**Frank, N. R., Cugell, D. W., Gaensler, E. A., and Ellis, L. B.: Ventilatory Studies in Mitral Stenosis. A Comparison with Findings in Primary Pulmonary Disease.** Am. J. Med. **15**: 60 (July), 1953.

Pulmonary function studies performed in 62 patients with rheumatic heart disease in whom mitral stenosis was the predominant valvular lesion indicated that patients with asymptomatic mitral stenosis had normal ventilatory functions except for occasional increases in resting minute ventilation and ventilatory equivalents. As symptoms appeared and progressed, gradual reductions in maximal breathing capacity and total vital capacity occurred; the timed capacities were not greatly reduced; resting minute ventilation, respiratory rate and ventilatory equivalents rose slightly while tidal volumes decreased; the calculated mean effective alveolar ventilation was maintained throughout all stages of disability; the breathing reserve at rest and the walking index remained unaffected until disability was severe. Patients not infrequently complained of weakness, fatigue or dyspnea during exercise without showing diminished breathing reserve or increased dyspnea indices. There were symmetric decreases of inspiratory capacity and expiratory reserve volumes. The residual volume rose early, largely at the expense of the expiratory reserve. Total lung capacities were not reduced until the advent of congestive circulatory failure; at that stage all divisions of the lung volume were diminished. Cardiac enlargement, acute and chroniic pulmonary edema, pleural effusion, ascites and hepatomegaly were of varying importance in reducing the lung volume compartments. There was no gross impairment of the distribution of inspired gas within the lungs. The initial findings were largely ascribed to pulmonary rigidity attending pulmonary hypertension and the later findings to encroachments upon parenchymal tissue by both extrinsic and intrinsic congestive changes. The ventilatory defect was not considered a useful quantitative index of disability except in far-advanced disease. Pulmonary functional changes were compared to those occurring in primary diseases; in the latter diseases the defects more closely reflected disability.

HARRIS

**Del Greco, F., Olmsted, F., Masson, G. M. C., and Corcoran, A. C.: Graphic Measurement of Arterial Pressure in the Unanesthetized Rat.** J. Lab. & Clin. Med. **41**: 729 (May), 1953.

A method is described for the measurement of arterial pressure in unanesthetized rats which consists of graphic registration of the tail pulse and pressure in a proximal occluding cuff. The accuracy of the method was established by comparing simultaneous tail graphic and carotid arterial pressures at normal levels and at those hypertensive levels attained two or more minutes after the intravenous injection of renin. The indicated tail systolic pressure correlates closely with the average carotid pressures. A comparison of the tail graphic and microphonic methods was made. The microphonic method yielded lower pressures, which were also two or three times more variable than those graphically recorded. Objectivity is the outstanding advantage of the graphic method. The speed of operation of the graphic method is as great or greater than the microphonic method. The greatest disadvantage of the graphic method is the cost of the apparatus and in case of breakdown or electrical failure, its complexity.

Following injections of renin, adrenalin and noradrenaline it was observed that during the persistence of decreased tail pulse caused by any of these substances, the tail pressures are erroneously low, in relation to the central arterial pressure or that they are immeasurable.

MINTZ

**Van Bogaert, A., Van Genabeck, A., Nijssens, A., Van der Henst, H., and Vandael, J.: Direct Measurement of the Pulmonary Arterial Pressure by Puncture in Man.** Acta cardiol. **8:** 288 (Fasc. 3), 1953.

Impressed by the frequency of endocardial lesions found in dogs following cardiac catheterization the authors worked out a method for determination of the pulmonary arterial pressure by direct puncture. When a prominent pulmonary arterial segment is found at fluoroscopy the vessel can easily be reached by a long needle introduced into the second or third intercostal space close to the sternum and the pressure in the pulmonary artery can be measured by connecting the needle to an electromanometer. The advantages of this method as compared with cardiac catheterization are claimed to be technically better pressure curves, less discomfort for the patient and the possibility of repeated pressure determinations in the course of instituted therapy. The procedure is contraindicated when the pulmonary arterial segment is not visualized at x-ray examination, in the presence of abnormal blood clotting (for example, during treatment with anticoagulants) in elderly persons and patients with angina pectoris.

PICK

**Smelin, A., Burstein, J., Blinder, H., and Lubart, A.: Tachycardia and Spontaneous Flutter in an Adult.** Arch. Int. Med. **91:** 685 (May), 1953.

A case of spontaneous 1 to 1 auricular flutter with a ventricular rate approximately 300 beats per minute in a 61 year old man is presented. The diagnosis of 1 to 1 auricular flutter was confirmed by esophageal electrocardiograms taken at atrial levels and by the appearance of typical auricular flutter complexes in the standard leads when the ventricular rate had been slowed by the action of intravenous administration of phenylephrine (Neo-Synephrine) and lanatoside C (Cedilanid). The recently stated hypothesis that auricular tachycardia and auricular flutter are caused by an identical mechanism is discussed relative to elucidating the nature of supraventricular tachycardias at very rapid rates.

BERNSTEIN

**Lown, B., Wyatt, N. F., Crocker, A. T., Goodale, W. T., and Levine, S. A.: Interrelationship of Digitalis and Potassium in Auricular Tachycardia with Block.** Am. Heart J. **45:** 589 (April), 1953.

The relationship of digitalis and potassium in paroxysmal auricular tachycardia with block was studied in three groups of patients including six patients digitalized because of congestive heart failure, two patients with uremia digitalized because of left sided failure, and five patients with spontaneous auricular ectopic rhythm. Group I differed from group III in that the auricular tachycardia followed either significant increases in digitalis dosage, extensive weight loss after mercurial induced diuresis, renal potassium loss, or a combination of these factors. Paroxysmal auricular tachycardia with block is characterized by: (1) an auricular rate of 150 to 250 per minute, (2) varying degrees of atrioventricular block, (3) an isoelectric baseline between the P waves, (4) diminution of the auriculoventricular delay by exercise, (5) augmentation of the delay by vagal stimulation, and finally (6) a tendency for the tachycardia to persist for days or even months.

In group I, the oral or intravenous administration of potassium salts terminated the arrhythmia. In group II, the extraction of potassium by means of hemodialysis was associated with the development of the arrhythmia. In group III, potassium administration was without effect.

The authors conclude that paroxysmal auricular tachycardia with block is an auricular manifestation of digitalis intoxication and that potassium depletion sensitizes the auricles to the toxic action of digitalis.

RINZLER

**Elwell, L. H., and Bean, J. W.: Intestinal Blood Flow in Curarization.** Am. J. Physiol. **174:** 185 (July), 1953.

Blood flow was increased by intra-arterial *d*-tubocurarine in innervated and denervated perfused segments of dog's intestine. Tonus and rhythmic contractions were decreased. Increased flow depends on dilation of intestinal vessels and not on reduction in intestinal tonus and rhythmicity. Atropine inhibits tonus and rhythmicity with only minor increases in blood flow. Following atropine *d*-tubocurarine still markedly augments blood flow. Repeated doses of *d*-tubocurarine do not lose their effectiveness on intestinal vessels. This is different than skeletal muscle. The authors point out that the splanchnic vascular area is very important in the general circulatory response to curare.

OPPENHEIMER

**Brady, L. W., Cooper, D. Y., Colodzin, M., McClenathan, J. E., King, E. R., and Williams, R.: Blood Volume Studies in Normal Humans.** Surg., Gynec. & Obst. **97:** 25 (July), 1953.

The authors investigated the problem of accurate methods for the determination of plasma and total blood volumes. The procedures studied consisted of the use of iodinated human serum albumin,

Evans' blue dye method, and red blood cells tagged with radioactive phosphorus. They found that when iodinated human serum albumin was utilized, a three-sample withdrawal method gave the most consistent results.

When the three procedures were compared simultaneously in the same subject, the red blood cells tagged with radioactive phosphorus gave the lowest values, the iodinated human serum albumin, the middle values, and the Evans' blue, the highest.

It was concluded that in order to determine the total blood volume, it was necessary to add the red cell mass, measured by radiophosphorus tagged red blood cells, and the plasma volume, obtained with iodinated human serum albumin.

ABRAMSON

**Frau, G., Maggi, G. C., and Agostini, A.: An Experimental Study of A-V Conduction over Fibres of the Bundle of Kent.** Acta cardiol. **8**: 225 (Fasc. 3), 1953.

The authors repeated Kent's original experiments in new born rats in order to confirm in this species the presence of atrioventricular muscular connections which are capable of transmitting impulses. Transverse sections through the A-V junction, including the A-V node and sparing only a small muscle bridge on the right or left ventricular border completely interrupted A-V conduction and produced A-V dissociation. This proves that in the rat, during the first days of life, A-V conduction takes place as in all mammals through the Tawara system. Kent's interpretation of his experiments is considered to be erroneous since no accessory pathways of A-V conduction could be demonstrated. A possible explanation of his observations could be mechanical stimulation of the ventricles by the independent atrial systole.

PICK

**Alexander, N.: Effect of Constriction of the Abdominal Aorta on Femoral Pulse and Mean Pressure in Rabbits.** Am. J. Physiol. **174**: 179 (July), 1953.

Constriction of the aorta above the mesenteric artery sometimes increased mean femoral and carotid blood pressure. When femoral pressure was high the femoral pulse waves were not much damped. When femoral pressure is normal the femoral pulse waves are highly damped.

OPPENHEIMER

**Buckley, J. J., Van Bergen, H., Dobkin, A. B., Brown, E. B., Miller, F. A., and Varco, R. L.: Postanesthetic Hypotension Following Cyclopropane: Its Relationship to Hypercapnea.** Anesthesiology **14**: 226 (May), 1953.

The clinical syndrome of "cyclopropane shock" is characterized usually by a pronounced fall in blood pressure occurring immediately after cyclopropane anesthesia is stopped, and is often associated with pallor, weak slow pulse, and a cold clammy skin. The authors studied 31 patients subjected to light cyclopropane anesthesia with the portable mass spectrometer for the continuous measurement of alveolar carbon dioxide tension. Significant accumulation of alveolar carbon dioxide was found in 15 patients who were allowed to breathe spontaneously during anesthesia. At the same time an elevation of blood pressure was found. When anesthesia was stopped, these patients showed an immediate fall in carbon dioxide tension which was accompanied by a prompt and often marked drop in arterial blood pressure. There was a direct relationship between the degree of hypercapnea developed and the severity of this postanesthetic hypotension, but there was no correlation with the duration of the hypercapnea. Clinically these patients manifested other characteristics of the "cyclopropane shock" syndrome and in a few, hypotension persisted for 12 to 48 hours. In 16 other patients respiration during anesthesia was assisted by manual compression of the breathing bag in synchrony with their spontaneous exchange. In these patients a normal alveolar carbon dioxide concentration was maintained at all times. The arterial blood pressure rose during the anesthetic period, but this was variable and not related exclusively to carbon dioxide accumulation. When anesthesia was stopped, only two patients in this group showed a fall in blood pressure and this was not severe. These patients had a smooth recovery period. The authors believe that these findings substantiate the theory that "cyclopropane shock" is directly related to hypercapnea. Respiratory acidosis develops because the anesthesia depresses tidal exchange and high alveolar carbon dioxide tensions appear. This raises the threshold of the centers concerned with vascular homeostasis. With subsequent rapid elimination of carbon dioxide a fall in blood pressure results because of the altered threshold in the medullary cells. These findings point to the necessity of maintaining adequate pulmonary ventilation during cyclopropane anesthesia in order to prevent a postanesthetic hypotension. This may be done by rhythmic manual compression of the breathing bag by the anesthiologist.

SAGALL

**Hall, P. W.: Effects of Anoxia on Postarteriolar Pulmonary Vascular Resistance.** Circulation Research **1**: 238 (May), 1953.

In dogs the left lower pulmonary lobe was perfused in situ by blood directly from its carotid artery under conditions of regulated arterial pressure. The volume of ventilation was kept constant and anoxia could be produced by inflating the lung with nitrogen instead of room air. Determinations of venous outflows were made under the conditions

studied. The results indicate that the reduction of alveolar oxygen induced a slight but definite increase in pulmonary vascular resistance. From the nature of the experimental arrangement this increase in resistance must occur beyond the pulmonary arterioles.

SAGALL

**Awapara, J.: Oxidation of *l*-Glutamic Acid by Rat Heart.** Proc. Soc. Exper. Biol. & Med. **83:** 367 (June), 1953.

The results clearly indicate that glutamic acid is oxidized by heart homogenates. It is oxidized only after transaminating with oxalacetic acid and the resulting $\alpha$-ketoglutaric acid is then oxidized by way of the Krebs' cycle.

MINTZ

**Bashieri, L., and Ferri, F.: The Dynamics of Systole in Extrasystoles with Special Reference to Conditions Initiating Extrasystoles.** Ztschr. Kreislaufforsch. **42:** 203 (March), 1953.

In order to study the disturbance of cardiodynamics in connection with premature ectopic beats, the authors recorded, simultaneously, the electrocardiogram and the phonocardiogram in 26 patients with this disturbance of rhythm. From these curves the following data were obtained: the duration of the total systole, the time of isometric contraction, and the time of ejection of premature beat, the normal beat preceding it, and the one following it.

A premature contraction is characterized by a prolongation of the isometric phase and by a shortening of the ejection phase. The degree of the latter alteration increases with the degree of prematurity. The beat preceding the premature beat may have a normal, a prolonged, or a shortened time of isometric contraction. On this basis two principal types of premature beats can be distinguished: those elicited by a primary sudden disturbance of cardiodynamics, occurring in diseased hearts; and those preceded by an entirely normal contraction, which must be ascribed to an increased irritability of the myocardium and are termed by the author "autochtone extrasystoles."

The first beat which follows the pause after a premature beat may or may not compensate for the disturbance of dynamics. This compensation consists in a shorter time of isometric contraction and an augmentation of stroke volume of the first post-extrasystolic beat. Failure of such compensation to occur acts as a trigger mechanism for another premature beat. The authors believe that the distinction of the two types of premature beats, a "hemodynamic" and an "autochtone" one is important from the clinical and pathogenetic viewpoint.

PICK

**Glatt, R.: The Electrocardiogram of Flying Pilots Transmitted by Radio.** Cardiologia **22:** 238 (Fasc. 4), 1953.

A method is described for wireless recording of electrocardiograms of pilots during flight. The transmission is achieved by means of a frequency modulating device connected to the standard aircraft radio transmitter. With this arrangement electrocardiograms can be recorded on the ground in one or in several leads without artefacts or atmospheric distortions. Several such tracings of pilots flying a "DeHavilland Vampire" are reproduced. The described method is appropriate for cardiologic-physiologic control of people flying in high altitudes.

PICK

## PHARMACOLOGY

**Enselberg, C. D., Brodoff, B. N., and Griboff, S. I.: The Action of a New Oral Preparation of Digitalis, Acetyldigoxin.** Am. Heart J. **45:** 909 (June), 1953.

Acetyldigoxin is derived from lanatoside C by splitting off the glucose molecule. This drug was given orally to 26 patients with heart disease due to rheumatic fever, hypertension, or arteriosclerosis. Four patients had thyrotoxicosis in addition. Twenty-three were in congestive failure and the same number had auricular fibrillation. The effects of single doses of 2 and 3 mg. of acetyldigoxin orally were observed in these undigitalized patients over periods of six hours to two weeks. Subsequent doses to achieve and maintain a state of digitalization were determined according to the patients' clinical responses rather than by a predetermined course. The authors found that the recommended initial single digitalization dose be 2 mg., followed by 0.5 mg. doses at intervals of six to eight hours until a satisfactory effect is achieved. Maintenance can be accomplished by daily doses of 0.4 to 0.7 mg. The effects after a single dose of 3 mg. become manifest in about two hours and maximal in seven hours. Dissipation is complete in nine days. These effects are determined by the fall in rate of the patient with auricular fibrillation and its subsequent return to the control level.

RINZLER

**Weisman, S. A.: Review and Evaluation of Quinidine Therapy for Auricular Fibrillation.** J.A.M.A. **152:** 496 (June 6), 1953.

Any therapeutic agent that has been the subject of as much controversy as has quinidine deserves frequent reevaluation. The author discusses its use in ambulatory patients and reviews the studies on excretion and concentration in the body. This drug increases the PR, QRS, and QR conduction time and if administered in toxic doses, it may result in asystole. Overdosage has resulted in paralysis of the respiratory center with sudden death. Because a

good number of patients achieve normal rhythm with very small oral doses it is thought better to initiate treatment with such doses to avoid toxic symptoms. One cannot adhere to a predetermined schedule without courting trouble because variations in peak blood levels have been great. The risk of intravenous administration should be undertaken only in very severe types of arrhythmia where death appears to be imminent unless emergency measures are adopted. Intramuscular administration is advantageous in some instances such as cases in which oral use results in gastrointestinal symptoms, for patients in coma, and as a prophylactic and therapeutic measure for cardiac arrhythmias during surgery and anesthesia. The author feels that a fibrillating heart is not a fully compensated one and since quinidine is a myocardial depressant it is dangerous to use without first digitalizing the patient. This drug may again fall into disrepute should the laboratory be used as the guide for dosage instead of the patient's clinical reaction.

KITCHELL

**LeWinn, E. B.: Gynecomastia During Digitalis Therapy.** New England J. Med. **248:** 316 (Feb. 19), 1953.

This report adds eight cases to six previously reported by this observer of gynecomastia occurring in male patients who were receiving digitalis for myocardial insufficiency. The breast manifestations included pain associated with a disk-like swelling, subsidence of symptoms and signs in five patients when the drug was stopped and recurrence with resumption of the drug, and gradual diminution of the breast enlargement after several months of continued digitalis treatment. The digitalis preparations used included digitoxin, lanatoside C and powdered digitalis leaf. There was no correlation between the size of the dose, the type of digitalis nor the duration of treatment and the degree of breast involvement. The gynecomastia developed only after prolonged digitalis medication and when compensation appeared to have been reestablished. Fundamental chemical similarities between digitalis glycosides and steroidal hormones, cholesterol and the vitamins D are described. It is mentioned that in conditions such as congestive failure in which hepatic function is impaired any estrogen-like effect of the digitalis steroids may be intensified. A relative lack of adrenal and testicular androgens in older males may also enhance the estrogenic activity of digitalis aglycones.

ROSENBAUM

**St. George, S., Friedman, M., and Ishida, T.: Intracellular Distribution of Digitoxin.** Proc. Soc. Exper. Biol. & Med. **83:** 318 (June), 1953.

This work deals with the possible intracellular fate of digitoxin administered to the intact animal (rat). This type of experiment has never been done because of the technical difficulties heretofore involved in such a study. In view of the uncertainty concerning both the site and mode of action of this glycoside, such information might be of considerable value. This is particularly true, since the intracellular site of various enzymes now has been determined with a high degree of certainty.

The hearts and livers of animals given intravenous digitoxin were homogenized and separated by centrifugation into nuclear, mitochondrial and homogeneous supernatant fractions.

The results indicate that although digitoxin when administered to the intact animal was capable of entering the various cellular components, it appeared to concentrate (85 per cent) only in that fraction of liver and heart containing the soluble constituents of the cell and extracellular fluid. The trace amounts of digitoxin found in the nuclear and mitochondrial fractions suggest that digitoxin probably does not exert its characteristic action either at these intracellular stations or upon the energy producing enzyme-substrate complexes found therein.

MINTZ

**Masbernard, A., and Camelin, A.: Determination of the Circulation Time by Lobelin.** Klin. Wochenschr. **31:** 455 (May), 1953.

Lobelin in a rapid intravenous injection of 0.05 mg per kilogram causes a short attack of coughing and/or a short period of apnea. The interval between injection and the appearance of the reaction corresponds to the circulation time between cubital veins and the carotid sinus.

In 632 determinations on 295 patients the following average values were obtained: In normals 9.9 seconds, in neurotonics 6.5 seconds, in heart disease without clinical evidence of failure 10.3 seconds, in the presence of heart failure 23.7 seconds, in hypertension 11.5 seconds, in obesity 7.5 seconds, and in emphysema or chronic pulmonary disease without heart failure, 14.5 seconds.

The lobelin circulation time was invariably prolonged in the presence of heart failure, whether clinical manifestations were evident or not. Under the latter circumstances, the determination of the circulation time is of greatest value. It is further of importance in the prognostic evaluation of the patient and for the assessment of the effect of simple bedrest and of medical treatment. In no instance did injection of lobelin cause an alteration of the pulse rate or blood pressure, or discomfort of the examined person.

PICK

## PHYSICAL SIGNS

**Calenda, D. G., and Uricchio, J. F.: Superior Vena Cava Syndrome.** Arch. Int. Med. **91:** 800 (June), 1953

The second case in the world literature of superior

vena cava syndrome secondary to a dissecting aneurysm of the thoracic aorta is reported. The presence of chest pain radiating to the abdomen in a patient with superior vena cava syndrome should make one consider the diagnosis of dissecting aneurysm of the thoracic aorta.

Superior vena cava syndrome may have a sudden and dramatic onset or it may develop insidiously. In any case, with an acute onset one should attempt to distinguish between simple obstruction of this great vein and obstruction secondary to perforation of an aortic aneurysm into the superior vena cava, resulting in aorticocaval fistula. Both are characterized by the sudden appearance of cyanosis and edema of the face, neck, and upper extremities. Distended veins appear in these areas. The venous pressure becomes elevated. Dyspnea, orthopnes, and cerebral symptoms are common to both. However, in the presence of a communication between the aorta and the vena cava certain other signs appear, which are diagnostic of aorticocaval fistula. There is a machinery murmur in the third right intercostal space. A systolic thrill may be felt in approximately 5% of the cases. When the venous pressure is measured, the column in the manometer will oscillate with each systolic thrust. Signs of arteriovenous aneurysm, such as Corrigan's pulse, capillary and hepatic pulsations, and Duroziez' murmur will appear.

The differentiation of these two types of obstruction of the superior vena cava may have some clinical importance. With the rapid strides that are being made in cardiac surgery, it may be of value to know whether one is dealing with an aorticocaval fistula.

BERNSTEIN

**Briskier, A.: New Device for Objective Auscultation of the Heart: Permanent Audible and Visual Record of the Heart Acoustics.** Am. Heart J. **45**: 914 (June), 1953.

In order to register simultaneously the heart acoustics for visual and auditory reproduction, three known instruments are used: the electrocardiograph, the phonostethograph, and the electromagnetic tape recorder. The limitations, advantages and applications are discussed.

RINZLER

**White, P. D., Schaaf, R. S., Counihan, T. B., and Hall, B.: The Clinical Significance of Apical and Aortic Systolic Heart Murmurs (without Diastolic Murmurs) as Heard with the Stethoscope.** Am. J. Med. Sc. **225**: 469 (May), 1953.

Despite the introduction of many new technics for the study of the heart and circulation, the skillful use of the stethoscope remains the most valuable asset for the cardiologist. In the present study, evaluation of the intensity of systolic murmurs in a group of cardiac patients was made and the findings related to mortality and other clinical factors. There were 1777 cases with grades 2 and 3 murmurs, 187 with grades 4 and 5 murmurs, and 200 with no murmurs. The ratio of males to females (three to two) and the age incidence were the same for the three groups. Etiology of heart disease was predominately coronary artery or hypertensive disease; however, in those with the loudest murmurs rheumatic heart disease was found in 27 per cent. In about 20 per cent of the patients, the site of maximal intensity was the aortic area; the systolic aortic murmurs without a diastolic component did not have a poorer prognosis than did the apical systolic murmur.

It was found that those patients with the loudest murmurs suffered the highest mortality although 8 per cent of these patients were still alive 15 years after the murmur was first recorded. The male mortality in all groups was higher than the female. A background of coronary or hypertensive heart disease gave a higher mortality than did rheumatic heart disease. Cardiac enlargement was associated with a poorer prognosis in all cases. Enlargement of the heart apparently reflected the degree of strain produced by the valvular defect and the ability of the patient to resist such strain.

SHUMAN

## PHYSIOLOGY

**Parker, C. S., Breakell, C. C., and Christopherson, F.: The Radio-electrophysiologogram. Radio Transmission of Electrophysiological Data from the Ambulant and Active Patients.** Lancet **1**: 1285 (June 27), 1953.

The authors describe a radio transmitter which the subject carries and which is modulated by his electrocardiogram, electroencephalogram or other physiologic phenomena. The subject, completely mobile and free from constraining leads, can undertake any activity whose effect on the particular physiologic phenomenon is to be studied. Application to phonocardiography is suggested.

MCKUSICK

**Rodrigo, F. A.: The Determination of the Oxygen of Blood in Vitro by Using Reflected Light.** Am. Heart J. **45**: 809 (June), 1953.

A method for determination of the percentage of oxygen saturation of blood samples discovered by Brinkman and Zijlstra is discussed. The method is based on the fact that the intensity of light reflected by blood is dependent on the degree of oxygenation. The author describes the "Brinkman haemoreflector," discusses the reflection theory, modifies the haemoreflector and then compares it with the method of Van Slyke, with which there is good agreement. The standard deviation of the reflection method, from duplicate readings, is 1 per cent difference in oxygen saturation.

RINZLER

**Grafflin, A. L., and Corddry, E. G.: A Note on Peripheral Blood Vascular Beds in the Bulbar Conjunctiva of Man.** Bull. Johns Hopkins Hosp. **92:** 423 (June), 1953.

The authors described an endless variety in the vascular patterns observed in the peripheral vascular beds in the bulbar conjunctiva of man and found nothing suggesting an organization in terms of structural units of even an ill-defined nature.

McKusick

## RHEUMATIC FEVER

**Henderson, L. L.: Sodium Salicylate in Rheumatic Fever; Effect of Adjuvant Medication.** Am. J. Med. Sc. **225:** 480 (May), 1953.

The use of salicylates in the treatment of acute rheumatic fever is associated with certain side effects such as gastric irritation and a lowering of the carbon dioxide combining power. Sodium bicarbonate administered with the salicylates reduces gastric distress, but also has been shown to lower the blood salicylate levels. In the present study, the plasma salicylate level of patients receiving only sodium salicylates (1.6 Gm. daily) was 42.2 mg. per cent; in those receiving both salicylates and sodium bicarbonate, the plasma salicylate level was 29.8 mg. per cent. However, in the latter group the carbon dioxide combining power remained normal, whereas in the former, it fell to 40 volumes per cent. Magnesium trisilicate and aluminum hydroxide given with the salicylates prevented gastric distress and did not reduce the plasma salicylate level; however, the carbon dioxide combining power fell with these adjuvants. Enteric coated salicylate tablets are well tolerated in somewhat smaller than the above dosage. Massive doses of salicylates seldom result in any harmful effect but may cause discomfort.

Shuman

**Gray, F. D. Jr., and Gray, F. G.: Circulatory and Ventilatory Changes in Chronic Rheumatic Heart Disease with Mitral Stenosis.** Am. J. M. Sc. **225:** 605 (June), 1953.

The authors selected for study 13 patients with mitral stenosis under consideration for mitral valvulotomy. These individuals were subjected to cardiac catheterization for the determination of pressures within the heart, pulmonary artery, and capillaries, and for the collection of mixed venous blood for oxygen determinations. Pulmonary function studies were also performed for measurement of lung volumes, maximal breathing capacity, and functional residual capacity. From the data obtained, it was found that the mixed venous blood oxygen saturation and the rates of systemic blood flow were reduced in most cases. The values were somewhat lower in those receiving digitalis, probably because of more serious cardiac disease in this group. The calculated mitral valve area was below the normal value in each case. The increased resistance offered to blood flow through the stenotic valve resulted in the reduced rate of blood flow and a general increase in pressures within the pulmonary vessels and right heart. The elevated mean pulmonary capillary pressure probably produces edema of alveolar structures which may account for the dyspnea and orthopnea experienced by these patients. It is stated the cardiac catheterization has limited usefulness in the selection of patients for mitral valvulotomy since much of the information obtained is of doubtful accuracy.

Shuman

## ROENTGENOLOGY

**Von Ronnen, J. R.: The Roentgen Diagnosis of Calcified Aneurysms of the Splenic and Renal Arteries.** Acta radiol. **39:** 385 (May), 1953.

A review is given of the literature concerning the pathogenesis, roentgenologic diagnosis and treatment of aneurysms of the renal and splenic arteries.

The case histories of five patients in whom one or more calcified aneurysms were roentgenologically diagnosed are presented. The differential diagnoses between these and those of calcified aneurysms of other upper abdominal arteries, calcified cysts, renal pancreatic gall baldder calculi, calcified mesenteric nodes and tuberculosis foci are discussed. The author urges conservative therapy for small aneurysms, and surgical removal for larger ones causing localized pressure effects.

Schwedel

**Cignolini, P.: Possible Roentgenkymographic Demonstration of Coronary Pulsations.** Radiol. Prac. **3:** 100, 1953.

The author studied the possibility of direct roentgenkymographic registration of the pulsations of the coronary arteries. According to him, the various waves of the ventricular roentgenkymogram are due not only to changes of volume and positional changes but also to changes of the coronary blood flow. Pressure waves and changes of flow in the coronary system might cause rhythmic changes in thickness of the myocardial ventricular wall; these changes are supposed to be perceptible in the roentgenkymogram.

The "T wave" as now described is attributed to the acceleration of flow in the coronary system in early diastole, when the ventricular wall is relaxing and the blood permeates the ventricular myocardium.

Luisada

**Goodwin, J. F., Steiner, R. E., Mounsey, J. P. D., MacGregor, A. G., and Wayne, E. J.: A Critical Analysis of the Clinical Value of Angiocardiography in Congenital Heart Disease.** Brit. J. Radiol. **26:** 161 (April), 1953.

The value of angiocardiography is assessed and

evaluated in 118 cases of congenital heart disease. Death occurred twice (1.7 per cent) in association with this procedure, both were in deeply cyanotic patients under general anesthesia.

*Tetralogy of Fallot:* Early opacification of the aorta occurred in all cases. The degree of shunt could be estimated from the reopacification of the aorta from the left ventricle. The outlining of the aorta and subclavian arteries could be helpful to the surgeon. In 20 per cent of the cases the type and site of the pulmonary stenosis could not be ascertained accurately.

*Eisenmenger:* Early opacification of the aorta, and dilated pulmonary arteries occurred. Pulmonary parenchymatous congestion was present in four, and absent in two. In the latter two cases it was difficult to differentiate these from Tetralogy cases.

*Atrial Septal Defect:* Early filling of the left atrium in cases with pulmonary hypertension, dilated main pulmonary arteries, and right ventricular and atrial enlargement were observed.

*Transposition of the Great Vessels:* The aorta was seen to come off from the right ventricle. The pulmonary artery filled later than the aorta and in the left lateral position the pulmonary artery was anterior to the aorta.

*"Pure" Pulmonary Stenosis:* The site of localized obstruction was demonstrated in four of the five cases, best in the lateral views.

*Pulmonary Stenosis plus Atrial Septal Defect:* Early opacification of the left atrium was found. Valvular stenosis was demonstrable in three of the nine cases, infundibular stenosis in one. One patient, age 41, in addition had calcareous aortic stenosis, confirmed at autopsy.

*Pulmonary Atresia:* Absence of opacification of the main pulmonary arteries, usually associated with an abnormally large transposed overriding aorta was seen.

*Tricuspid Atresia:* Passage of contrast medium from the right to the left atrium, absence of right ventricular filling noted by a triangular area of increased illumination in the postero-anterior view where the right ventricle usually is noted was the picture presented here. Pulmonary artery filling occurred in the first case through bronchial arteries arising from a truncus arteriosus; in the second from a patent ductus arteriosus; in the third, through a ventricular septal defect.

*Ebstein's Anomaly:* Deformed tricuspid valves displaced into the right ventricle may be demonstrable. Enormous right atrial enlargement, poor visualization of the right ventricle, and pulmonary arteries are also important in the diagnosis.

*Coarctation of the Aorta:* The site of coarctation was demonstrable in all 15 cases. The extent of coarctation was evident in all but two. The aorta was dilated in five proximal to the obstruction, and in eleven distal to the stenosis.

*Patent Ductus Arteriosus:* This procedure added little to the clinical findings. Aortography is considered a more suitable method in doubtful cases.

SCHWEDEL

**Wegelius, C., and Lind, J.: The Role of the Exposure Rate in Angiocardiography.** Acta radiol. **39:** 177 (March), 1953.

The authors suggest that serial angiograms taken at rapid but stated intervals are less likely to indicate the physiology of atrial and ventricular emptying and filling than those correlated with electrocardiograms or some other suitable timing apparatus. Fast angiocardiography (12 films per second), and rapid exposure times (0.02 second) are required.

SCHWEDEL

**Gasul, B. M., Weiss, H., Fell, E. H., Dillon, R. F., Fisher, D. L., and Marienfeld, C. J.: Angiocardiography in Congenital Heart Disease Correlated with Clinical and Autopsy Findings.** Am. J. Dis. Child. **85:** 404 (April), 1953.

Based upon the correlation of angiocardiographic findings with clinical and pathologic findings in this series, the following conclusions may be stated regarding the value of angiocardiography as an aid in the clinical diagnosis of congenital cardiac malformations. The procedure is effective in indicating intracardiac and extracardiac shunts and abnormalities in size, shape, and position of the great vessels as well as of the cardiac chambers, and in visualizing abnormalities in the return of the great veins to the heart. Particularly in the young cyanotic infants, whose roentgenographic and electrocardiographic findings may be difficult to interpret and in whom cardiac catheterization may be difficult or impossible, angiocardiography is most useful. This procedure is of less value in the noncyanotic group of malformations, as left-to-right shunts are difficult to localize accurately. However, coarctation of the aorta is a noncyanotic condition which is effectively visualized.

It must be remembered that angiocardiography indicates only specific abnormalities of the heart, and therefore cannot be expected in itself to diagnose entire clinical syndromes. It must be viewed as merely another laboratory aid which is to be correlated with the history, physical examination, electrocardiography, roentgenography, fluoroscopy and cardiac catheterization, in order to arrive at a final and more complete diagnosis. By correlating the angiocardiographic findings with the clinical syndrome and the pathologic findings, such as was done in this study, the clinician's understanding of the pathology present is improved, and he is thus rendered more capable of diagnosing additional cases of the same type.

BERNSTEIN

**Lindgren, E.: Technique of Abdominal Aortography.** Acta radiol. **39**: 205 (March), 1953.

The author discusses some of the technical details and dangers associated with the direct puncture (Dos Santos) of the aorta in the left costovertebral space and also, retrograde abdominal aortography wherein a polyethylene catheter is passed up from a femoral artery. General anesthesia is preferred to local anesthesia because the fall in blood pressure generally aids arterial opacification. Local injury, extravasation, and sensitivity to the contrast substances must always be kept in mind, and when possible avoided.

SCHWEDEL

**Seldinger, S. I.: Catheter Replacement of the Needle in Percutaneous Arteriography. A New Technique.** Acta. radiol. **39**: 368 (May), 1953.

The author describes a method by which it is possible, after percutaneous puncture, to insert a catheter of the same size as the needle inserted into the artery. This is accomplished by inserting a flexible metal leader into the arterial puncture needle, extending it into the artery for several centimeters, and then replacing the external arterial needle by a polyethylene catheter of the same external diameter over the leader into the arterial lumen.

Forty arterial catheterizations have been performed: 35 aortographs through the femoral artery, three through the brachial artery, two femoral catheterizations distally. There were no untoward complications except for one moderate hematoma. The great advantage of this method is that, now, larger bore catheter tubing may be inserted whereas formerly, a catheter had to be smaller than the needle through which it had to be passed.

SCHWEDEL

## SURGERY IN HEART AND VASCULAR SYSTEM

**Werkö, L., Björck, G., Crafoord, C., Wulff, H., Krook, H., and Eliasch, H.: Pulmonary Circulatory Dynamics in Mitral Stenosis Before and After Commissurotomy.** Am. Heart J. **45**: 477 (April), 1953.

Pulmonary dynamics at rest and during exercise before and after surgical treatment were studied in 39 of 46 patients with rheumatic mitral stenosis who survived the operative procedure. The measurements obtained by direct catheterization and brachial artery sampling included the total pulmonary resistance, mean pressure of the pulmonary artery, pulmonary vascular resistance, and mitral valvular resistance. The best objective results from operation were obtained in cases below the age of 45 years, with sinus rhythm and heart size less than 600 ml. per square meter of body surface area and symptoms corresponding to group III or IV.

RINZLER

**DeBakey, M. E., and Cooley, D. A.: Successful Resection of Aneurysm of Thoracic Aorta and Replacement by Graft.** J. A. M. A. **152**: 673 (June 20), 1953.

A 46 year old white man with a huge, probably syphilitic, aneurysm of the descending thoracic aorta, producing extensive erosion of the vertebral bodies and incapacitating symptoms was operated upon. The aneurysm along with the involved segment of aorta was successfully resected with restoration of normal blood flow by means of an aortic homograft. Although the aorta was occluded for a period of 45 minutes during anastomosis, there were no residual manifestations of ischemic changes in the spinal cord, the kidneys, or other organs. The authors report that on May 2, 1953, the patient was continuing to show progressive improvement with complete relief of symptoms.

KITCHELL

**Thompson, S. A., and Plachta, A.: Experiences with Cardiopericardiopexy in the Treatment of Coronary Disease.** J. A. M. A. **152**: 678 (June 20), 1953.

For 13 years the authors have been treating a selected group of coronary patients with the operation known as cardiopexy. They present their experiences with 57 of these operations. The operative procedure of cardiopericardiopexy is accomplished by spreading sterile powdered magnesium silicate over the myocardium inside the pericardial sac (U. S. P. talc). This talc acts as an irritant which produces a talc granuloma involving the superficial surface of the myocardium. It stimulates the development of interarterial coronary anastomoses and produces adhesive pericarditis. Almost all the operative group of patients have been in the terminal state, medical failures, and were completely incapacitated. Very few of them were satisfactory surgical risks. In spite of these handicaps 90 per cent of them are more than 50 per cent improved, and 40 per cent are more than 75 per cent improved. The patients who have since died lived an average of five years after the operation, giving them an average life span of nine and one-half years from the onset of the first symptom. The authors do not believe these patients would have survived this length of time without the operation.

KITCHELL

**Chapman, D. W., Skaggs, R. H., Johnson, I. A., Mills, L. C., and Cooley, D. A.: Venous Catheterization of the Heart in Selection of Patients for Mitral Commissurotomy.** South. M. J. **46**: 343 (April), 1953.

Thirty-six cases of rheumatic heart disease have been studied by means of venous catheterization of the heart and cardiac output determination. Thirty have had commissurotomies with two deaths. Indications for valvulotomy as ascertained from venous

catheterization of the heart, which, of course, must be used in connection with a careful clinical evaluation of the patient, may be summarized as: elevated resting "pulmonary capillary" pressure increasing with exercise; elevated resting and exercise pulmonary arterial pressure; reduced resting cardiac output with little or only slight increase during exercise; arteriovenous oxygen difference elevated above normal, both in the resting and exercise states; increased pulmonary arteriolar resistance and total pulmonary resistance; and decreased mitral valve size as calculated by the formula of Gorlin and Gorlin.

BERNSTEIN

**Webb, A., Jr.: Some Technical Considerations in the Operative Treatment of Varicose Veins.** Ann. Surg. **137**: 778 (May), 1953.

A new type of vein stripper is described. It is made of ribbon steel and has a natural curve and a small obturator end. The natural curve and the ribbon construction are of value in altering the course of the stripper when the obturator enters a branch or becomes impinged upon a sacculation. The apparatus can be used for the treatment of varicosities of the lesser as well as of the greater saphenous veins. In most instances only two incisions are necessary for each vessel.

The patients begin walking about eight hours after operation and then every two hours thereafter while awake. They are sent home from the hospital the day after surgery. The use of elastoplast and ace bandages helps prevent edema.

ABRAMSON

**Vineberg, A., and Miller, D.: Functional Evaluation of an Internal Mammary–Coronary Artery Anastomosis.** Am. Heart J. **45**: 873 (June), 1953.

The internal mammary coronary artery anastomosis is carried out in dogs by freeing the left internal mammary artery from the chest wall from the fourth to sixth intercostal space. The distal end is doubly ligated and transected. The artery is implanted into a tunnel made in the anterior wall of the left ventricle. The intercostal vessels which arise from the freed portion of the internal mammary artery are ligated except for the sixth which is transected just before the implant is pulled into the myocardial tunnel. The anatomic basis for the value of this procedure lies in two factors: (1) the peculiarly rich network of blood vessels which supply the myocardial muscle fibers; and (2) the pathologic finding that arteriosclerosis of the coronary arteries is usually, if not always, confined to the epicardial part of their courses and never involves the penetrating myocardial branches to any significant degree.

Proof of the presence of anastomosis between the implanted mammary artery and the left coronary circulation was established by injection studies, radiographs, serial sections, and plastic casts. Twenty-nine animals with successful implants survived ligation of the anterior descending branch of the left coronary artery 100 per cent even without infarction. Thirty-nine animals with internal mammary implants and/or other experiments but without augmentation of the coronary circulation following left coronary artery ligation suffered 80 per cent deaths, 3 per cent survival with infarction and 17 per cent survival without infarction. Ten control animals after coronary artery ligation sustained 80 per cent deaths and twenty per cent survival with infarction. Ligation of the internal mammary artery in animals surviving left coronary artery ligation resulted in two deaths and one survival. The presence of recent infarcts in the animals that died indicated that the mammary artery was supplying blood to the anterior portion of the left ventricle.

Coronary artery insufficiency was produced by wrapping Cellophane around a segment of the left coronary artery from 4 to 8 mm. long. The resulting fibroplastic reaction with collagen deposition resulted in a narrowing of the arterial lumen and ischemia of the myocardium usually supplied by this vessel. Exercise tests on a treadmill in such dogs before and after experimental coronary insufficiency was produced showed a decrease in exercise tolerance after Cellophane wrapping. A subsequent internal mammary artery implant was able in some animals to return the exercise tolerance to the control level.

RINZLER

**Stead, W. W., Martin, R. E., and Jensen, N. K.: Physiologic Studies Following Thoracic Surgery IV. The Mechanism of the Development of Acidosis during Anesthesia.** J. Thoracic Surg. **25**: 435 (May), 1953.

Total ventilation, alveolar ventilation, arterial blood pH and $P_{CO_2}$ were determined before and throughout the period of anesthesia in 13 patients who underwent major thoracic surgical procedures. Most patients developed respiratory acidosis, manifested by a significant increase in $P_{CO_2}$ with a decreased blood pH. There was no correlation between the total ventilation and the $P_{CO_2}$ ($r = 0.094$). There was, however, a reciprocal relationship between alveolar ventilation and $P_{CO_2}$. When the anesthesiologist prevented a fall in alveolar ventilation acidosis was averted. The data suggest that the major factor responsible for the acidosis which occurs during anesthesia is inadequancy of alveolar ventilation.

MAXWELL

## THROMBOEMBOLIC PHENOMENA

**Brown, K. W. G., and MacMillan, R. L.: The Anticoagulant Effect of Phenylindanedione in Thrombo-embolic Disorders.** Am. J. Med. Sc. **225**: 495 (May), 1953.

The effect of phenylindanedione on the plasma prothrombin level was studied in a group of 143 patients with thromboembolic diseases such as pulmonary infarction, myocardial infarction, and phlebothrombosis. The drug was found to produce satisfactory depression of prothrombin in most cases within 48 hours; its effect was dissipated upon discontinuance in about two days. The maintenance of prothrombin times within the therapeutic range was not as satisfactory as with Dicumarol or Cyclocumarol. However, this difficulty may have arisen from inadequate dosage schedules employed. There were no bleeding manifestations in the patients reported, although two other patients were seen who had bled into their surgical incisions while on the drug. The dark orange discoloration of the urine, mistaken for hematuria, was thought to be an excretion product of phenylindanedione. Vitamin $K_1$ and $K_1$ oxide were found to restore safe prothrombin levels within four to five hours when administered to these patients.

SCHUMAN

## VASCULAR DISEASE

**Lodwick, G. S.: Dissecting Aneurysms of the Thoracic and Abdominal Aorta. Report of Six Cases, with a Discussion of Roentgenologic Findings and Pathologic Changes.** Am. J. Roentgenol, **69:** 907 (June), 1953.

The author discusses the pathologic and clinical features of aortic rupture with dissection, and presents six cases proven at autopsy. The following types of dissecting aneurysms are described: first, the classic with cystic degeneration or medionecrosis, usually arising in the supravalvular portion of the aorta, or just at or beyond the aortic isthmus; and second, the arteriosclerotic type, most frequently abdominal, less frequently thoracic wherein the dissection is usually much less extensive than in the medionecrotic type.

Six cases of dissecting aneurysm are presented. Three dissected extensively and involved the abdominal as well as thoracic aorta and great vessels. Re-entry of the dissection into the aorta occurred in all of these. Of the three cases of arteriosclerotic etiology, two occurred in the thorax, one in the abdomen. Both aneurysms of the arch originated in calcified intimal atheroma. The frequency of aortic calcification associated with dissecting aneurysm apparently is a notable feature.

SCHWEDEL

**Semple, R.: Diabetes and Peripheral Arterial Disease. A Clinical Study.** Lancet **1:** 1064 (May 30), 1953.

The author was surprised to find only 6 instances of diabetes among 100 patients with intermittent claudication. Subsequent study of the peripheral circulation in 100 diabetic patients revealed that arterial disease in this group more often presented itself with gangrene than with intermittent claudication. Evidence from several sources suggests that this mode of manifestation is related to predilection for involvement of more distal arteries of the leg and foot.

MCKUSICK

**Blakemore, A. H.: Progressive Constrictive Occlusion of the Aorta with Wiring and Electrothermic Coagulation for the Treatment of Arteriosclerotic Aneurysms of the Abdominal Aorta.** Ann. Surg. **137:** 760 (May), 1953.

The author summarized the results of his experience in the treatment of abdominal aortic aneurysms using wiring and electrothermic coagulation, in conjunction with banding of the aorta. Death occurred in 17 of 32 cases; in nine of these, the cause was subsequent rupture of the aneurysm. It was believed that the poor results were due to inadequate banding of the aorta, thus producing more serious strain upon the aneurysm.

Despite the relatively high mortality associated with operation, the author recommended that all patients with arteriosclerotic aneurysm of the abdominal aorta be evaluated for surgery, since the incidence of rupture and death under medical management was much higher.

ABRAMSON

**Howe, C. W., and Wigglesworth, W. C.: Control of Infections Associated with Obliterative Arterial Disease.** Surg., Gynec. & Obst. **96:** 553 (May), 1953.

The authors studied various means of controlling local infection associated with nutritional disturbances of the lower extremities, due to an obliterative arterial disease. Besides the use of systemic antibacterial agents, solutions of these substances were also applied topically after the lesion had been debrided. In order to maintain continuous contact of the tissues with the drugs, the solutions were fed through no. 8 or 10 French rubber catheters. Although some wrinkling of the surrounding normal skin occurred, maceration of the tissues was not encountered, since only small quantities of the antibiotic solutions were found to be adequate.

Control of the local infection frequently led to healing. However, if only partial epithelization took place, the poor response was considered to be due to the vascular component of the disease. Where the latter predominated, antibiotics were of little value in producing improvement in the lesion or in preventing its spread.

ABRAMSON

**McGarity, W. C., and Robertson, R. L.: Arterial Embolism with Notes on Operative and Anticoagulant Therapy.** Surg., Gynec. & Obst. **96:** 522 (May), 1953.

A case is reported of multiple arterial embolism, in each instance treated surgically, with salvage of the involved extremities. The site of origin of the emboli was evidently a mural thrombus associated with a recent myocardial infarction.

The first embolus lodged at the bifurcation of the right common femoral artery. This was removed surgically 12 hours after the onset of the symptoms. However, propagation had occurred distally, and it was therefore necessary to expose the posterior tibial artery and insert a large metal cannula pointed proximally. The distal arterial tree was then forcefully irrigated with a solution of heparin. This maneuver, plus gentle milking of the superficial femoral artery, caused a long distal thrombus to be extruded through the opening in the common femoral artery. The second embolus lodged in the left common femoral artery about six days postoperatively. This was also removed surgically with excellent results.

About two months later there was a recurrence of embolization, this time again involving the right femoral artery at its bifurcation. An arteriotomy was performed, with removal of an embolus. However, since the artery was quite thin, the affected segment was removed and the continuity of the vessel was reestablished by means of a vein graft. The patient remained on anticoagulants for six months. During this period the circulation in both lower extremities remained normal.

ABRAMSON

**Bigelow, N. H.: The Association of Polycystic Kidneys with Intracranial Aneurysms and Other Related Disorders.** Am. J. M. Sc. **225:** 485 (May), 1953.

The author contributes three additional cases to the literature of the associated findings of intracranial aneurysms and polycystic renal disease. In reviewing this subject, it was found that nearly 10 per cent of the patients with polycystic renal disease have intracranial aneurysms, an incidence which suggests some common pathogenic developmental defect. The patients described in this report were 33, 62, and 52 years of age at the time of death which was caused by subarachnoid bleeding, renal failure, and bronchiogenic carcinoma respectively. Other anomalies found in association with polycystic kidneys include coarctation of the aorta, biliary cysts of the liver, and cysts of the pancreas, lung, and spleen. The author suggests that polycystic renal disease may be one phase of a disseminated congenital disorder analogous to tuberous sclerosis, neurofibromatosis or Lindau-Von Hippel's disease.

SHUMAN

**Baird, McL.: Saccular Aneurysms of the Abdominal Aorta.** Arch. Int. Med. **626:** 91 (May), 1953.

Three cases of saccular aneurysm of the abdominal aorta with unusual clinical manifestations are described. The first case closely resembled that of a bleeding peptic ulcer, but death was due to rupture of an atheromatous aneurysm into the ileum. The literature on this subject is briefly reviewed. The patient in the second case was thought on admission to have a bleeding peptic ulcer and uremia, but autopsy confirmed the presence of an abdominal aortic aneurysm causing pressure on the left ureter and renal vessels and left-sided hydronephrosis. The third case was clinically recognizable as a ruptured abdominal aneurysm, but the electrocardiogram suggested an anterior coronary occlusion. At autopsy a huge peritoneal hematoma from a ruptured aneurysm was found. The coronary vessels although narrowed were patent. The reasons for the bizarre electrocardiogram are discussed and the literature is reviewed.

BERNSTEIN

**Hershey, S. G., Zweifach, B. W., and Rovenstine, E. A.: Effects of Depth of Anesthesia on Behavior of Peripheral Vascular Bed.** Anesthesiology **14:** 245 (May), 1953.

The effect of the depth of anesthesia of cyclopropane, ether, or pentothal sodium was studied in each of three groups of five normal dogs. The depth of anesthesia was estimated clinically and studied as light, moderate, and deep. Observations of the peripheral circulation were made by blood pressure determinations from the femoral artery and direct microscopic observation of an exteriorized portion of the omentum. The following were studied to determine the influence on the circulation by varying the depth of anesthesia: (1) the reactivity of the terminal arterioles and precapillaries to topically applied epinephrine; (2) the periodic spontaneous muscular activity in the metarterioles and precapillaries; (3) the caliber of the terminal arterioles; (4) the capillary-venous outflow; (5) the rate of recovery of the above to the initial control levels; and (6) the arterial blood pressure. Ether, cyclopropane, and sodium pentothal were all found to exert a deleterious effect on the functional efficiency of the peripheral vascular circulation and its readjustment mechanisms within the capillary bed. This became more evident as the depth of anesthesia increased. The disturbance in these mechanisms was most marked with ether, less so with sodium pentothal, and least with cyclopropane anesthesia. These agents predispose the organisms to development of irreversible phenomena in regard to the peripheral circulation following hemorrhagic hypotension. These observations also indicate that these anesthetic agents have an effect on the circulatory mechanisms which is basically different from that of the autonomic blocking drugs, since the former cannot protect against the consequences of circulatory stress.

SAGALL

**Halligan, E. J., Costello, J. L., and Lewis, T. F.: Acute Massive Venous Occlusion of the Lower Extremity.** Ann. Surg. **137:** 543 (April), 1953.

Two cases were reported of acute massive venous occlusion of the lower extremity. In neither did gangrene occur. The characteristic findings were a rapid onset of severe, excruciating pain and of widespread and marked edema, progressive cyanotic mottling of the entire limb, and a high venous pressure locally. For treatment sympathetic denervation was carried out, using either epidural block or spinal anesthesia. Such an approach produced definite alleviation of symptoms and signs.

ABRAMSON

**Steiner, K., and Grayson, L. D.: Peripheral Vascular Failure as Cause of Death in Generalized Exfoliative Dermatitis.** J. A. M. A. **151:** 1479 (April 25), 1953.

Death in skin diseases occurs usually from infection, septicemia, toxemia, inanition, and exhaustion; involvement of the vital organs sometimes proves fatal. In 15 fatal cases of generalized exfoliative dermatitis previously described in the literature, 8 of the patients died of bronchopneumonia, 3 of cardiac failure, 1 of lobar pneumonia, 1 of anemia, and in 2 the dermatitis was reported as the cause of death. Peripheral circulatory collapse seems rarely to be the cause of death in exfoliative dermatitis although in some reports there are vague suggestions of the presence of shock. Particularly in generalized exfoliative drug dermatitis and in eczema of infants a collapse of the peripheral circulation seems frequently to be the immediate cause of death. The authors report four deaths from irreversible peripheral circulatory collapse. Degenerative changes in the adrenal cortex were found in the three patients in which autopsies were performed and the adrenal cortical failure manifested by these changes was believed responsible for the peripheral circulatory failure. Repeated use of cortisone and corticotropin in two of the four cases could also have been responsible for the occurrence of such collapse by inducing adrenal cortical failure. However, this would be a precipitating factor rather than the main cause since there can be no doubt that the disease per se produced the major stress effect in the other two cases reported. It is suggested that the use of cortisone and corticotropin should be strictly controlled in cases of generalized exfoliative dermatitis and the dosage kept as low as possible.

KITCHELL

**Milch, L. J., Redmond, R. F., Calhoun, W. W., and the Cardiovascular Research Group: Plasma Lipoprotein Changes Induced by Acute Local Cold Injury.** Am. J. M. Sc. **225:** 416 (April), 1953.

A group of 60 rabbits was employed in this study, with half the group exposed to severe cold injury involving one extremity, and the other half serving as controls treated in the same manner but without immersion into cold. Blood was obtained before and after the procedures for chemical and physiochemical analysis. The plasma cholesterol, transported in blood as a protein conjugate, was markedly increased in the traumatized animals. Significant increases were noted in the plasma concentration of the $S_f$ 12–20 and $S_f$ 20–100 classes of lipoproteins. These changes were not the result of hemoconcentration as established by the fact that there was no significant change in the packed-cell volume or total protein concentration of the blood plasma. Previous observations on liver injury showed that the conversion of acetate to cholesterol was increased several hundred fold in hepatic damage. It is suggested that the tissue cells synthesize increased amounts of cholesterol as an integral part of the repair process and that the higher level of plasma lipoprotein observed originated in the regenerating tissue of the traumatized rabbit legs.

SHUMAN

**Marks, C., and Fehler, B. M.: Aortic Occlusion in Infancy.** Brit. M. J. **1:** 709 (March 28), 1953.

The authors describe a case of in situ thrombosis of the aortic bifurcation in an 11 month old infant. The thrombosis, which was fatal in spite of paravertebral block and thrombectomy, occurred during acute fulminating bronchopneumonia.

MCKUSICK

## OTHER SUBJECTS

**Rodbard, S., Bolene-Williams, C., Pick, R., and Katz, L. N.: The Beneficial Effects of Intermittent Dietary Regimes on the Tendency to Atherosclerosis.** J. Lab. & Clin. Med. **41:** 587 (April), 1953.

The effect of intermittent feeding of cholesterol diets on the tendency to develop hypercholesteremia and atheromatosis was studied in chicks.

The continuous feeding in chicks of a diet supplemented with cholesterol resulted in an elevated plasma cholesterol level and in the production of aortic and coronary atherosclerosis. A diet of comparable chicks was arranged so that an equivalent amount of cholesterol was ingested in interrupted intervals. In the latter group of chicks, the plasma cholesterol rose rapidly during the periods of cholesterol feeding and the animals sacrificed at the end of these periods showed moderate development of atherosclerosis. Rapid reductions in the plasma cholesterol were observed when the chicks were on normal diets and the animals sacrificed at the end of this period had little or no atherosclerosis. The chicks which were fasted or given an oil-rich diet during the intermittent period showed only a slight tendency for a fall in the plasma cholesterol and little or no protection against atheromatosis.

These studies suggest that in the chick, intermittent periods of freedom from cholesterol feeding

may offer a degree of protection against the atherogenic effects of diets high in cholesterol.

MINTZ

**Bronstein, L. H., Goldwater, L. J., and Kresky, B.: Occupational Potentialities of the Older Cardiac Patient.** Geriatrics **8:** 252 (May), 1953.

Through the application of selective placement technics and with a reasonable amount of medical supervision, a considerable proportion of cardiac cases in the sixth and seventh decades can enter into and remain in useful employment.

Studies made in cardiac clinics have shown that a great majority of patients attending these clinics are engaging in useful occupations. Even among the older age groups, a substantial number is gainfully employed, and follow-up studies give no evidence that continuing employment has an adverse effect on the course of heart disease.

BERNSTEIN

**Man, E. B., and Peters, J. P.: Variations of Serum Lipids with Age.** J. Lab. & Clin. Med. **41:** 738 (May), 1953.

The serum lipid of 16 subjects, 7 males and 9 females, were remeasured after intervals of 10 to 20 years. The only basis of selection was the availability of the subjects. Their ages varied from 20 to 48 at the time of the initial observations, and from 30 to 65 years at the final observations. None of the subjects had any known metabolic disorders and all were leading active lives.

Total fatty acids, lipid phosphorus and cholesterol values of the serum revealed no consistent change between the age groups. Although these values rose significantly more frequently than they fell, this tendency was not sufficiently preponderant to warrant the deduction that it is characteristic of the aging process.

MINTZ

**Swann, R. C., and Merrill, J. P.: The Clinical Course of Acute Renal Failure.** Medicine **32:** 215 (May), 1953.

The authors briefly review recent contributions to the understanding of acute renal failure, and present a broad and detailed view of the clinical course based on a study of 85 cases. They point out that often the condition is not recognized at first because of the physician's preoccupation with the associated illness. Differential diagnosis is considered in detail.

During the oliguric phase the chief symptomatology is that of cardiovascular, gastrointestinal, and neuromuscular dysfunction. The most important clinical advance of the past 10 years is the recognition that after the onset of acute renal failure, cardiac function and not renal function should be the major concern of the clinician. Cardiac dysfunction is the most serious complication and the chief cause of death. Two forms of cardiac dysfunction are seen; the first culminating in pulmonary edema, and the second being associated with potassium intoxication.

It is unusual for cardiac function to remain unaffected, and early signs of dysfunction may be overlooked. These include tachycardia, heaving precordium, increased pulse pressure, accentuated second pulmonic sound, apical systolic murmur, and alteration in quality of the heart sounds. More serious signs include gallop rhythm, dyspnea, rales, cardiac enlargement, and pericardial friction rub. The outstanding blood pressure change is systolic hypertension and increased pulse pressure. There is no apparent correlation between the hypertensive changes and sodium metabolism except that a positive sodium balance may contribute to the development of hypertension. Pulmonary congestion is a frequent and ominous complication, and may progress to pulmonary edema even in cases in which salt and water have been more or less restricted. After prolonged oliguria during which only small amounts of dextrose have been given, the administration of small amounts of sodium or of whole blood may precipitate pulmonary congestion. Signs of cardiac failure may occur without hypertension, and in cases where excessive amounts of sodium or hypertonic solutions have not been given. Digitalis does not appear to result in striking improvement in the signs of cardiac failure. The authors express increasing reluctance to use hypertonic solutions of sodium for the sake of correcting hyponatremia because of the frequent complications of cardiac failure.

Signs and symptoms of potassium intoxication seldom appear before the condition is advanced and close to a fatal outcome. Adequate warning may be derived from both serial electrocardiograms and serum potassium and sodium determinations. The usual sequence of electrocardiographic signs of increasing hyperkalemia are increased amplitude of T waves with peaking, depression of S-T segments, decreasing height of R waves, prolongation of QRS and P-R intervals, diminution and disappearance of P waves, then of T waves, and merging of QRS and T into a broad sine-like wave. Associated bradycardia, arrhythmias, abnormal ventricular rhythms, and asystoles may appear. The physical signs of faint heart sounds, falling blood pressure, bradycardia and arrhythmias, weakness, hyporeflexia, apprehension, sweating, stupor and convulsions or paralysis of limbs and respiration are very late evidences.

Hyperkalemia occurred in most of the authors' cases. In only one fourth of the cases did the serum potassium remain below 5.5 mEq. per liter. Death occurred in 60 per cent of the men and 30 per cent of the women, the major cause being cardiac failure. About 25 per cent of the deaths occurred after the onset of diuresis. Treatment is discussed in case reports and considered in general.

ENSELBERG

**Popkin, R. J.: The Arteriolar Circulation as a Factor in the Results Obtained in Sympathectomy for Peripheral Arterial Occlusive Disease.** Angiology **4:** 210 (June), 1953.

The author states that although lumbar sympathectomy is a valuable treatment for peripheral arterial occlusive disease, he has observed many instances in which the procedure aggravated the clinical course or resulted in no demonstrable change. A therapeutic failure may follow favorable preoperative testing and conversely a therapeutic success may be found where preoperative testing indicated failure.

To explain aggravation of the clinical course following sympathectomy, it is postulated that sympathetic denervation produces an increased capacity of the arteriolar bed which cannot be met by an adequate arterial inflow because of severe arterial obstruction in the main vessels and an inadequate collateral circulation. Blood flow becomes retarded and thrombosis is encouraged.

WESSLER

**Wilson, H. C.: Denervation and Rhythmic Contractions of the Main Artery of the Rabbit's Ear.** J. Physiol. **174:** 162 (July), 1953.

Combined sympathectomy and parasympathectomy prevented rhythmic contractions of the main artery of the rabbit's ear but either one alone did not do so. After sympathectomy dilation was prolonged, and the reverse was true after parasympathectomy.

OPPENHEIMER

**Rushmer, R. F., Crystal, D. K., Wagner, C., and Ellis, R. M.: Intracardiac Impedance Plethysmography.** Am. J. Physiol. **174:** 171 (July), 1953.

When electrodes are implanted *within* the dog's heart the impedance between varies synchronously with the cardiac cycle. Records resemble those made with a cardiometer. Impedance increased during systole and decreased during diastole. Thus impedance was inversely related to the distance between the electrodes. As a result, intrathoracic tissues are not a homogeneous conducting medium. The animal's position changed the amplitude and configuration of the recorded curves.

OPPENHEIMER

**Gottlieb, A. M., Baer, L. J., and Jordan, P.: Mediastinal Lipoma Simulating Cardiac Enlargement.** J.A.M.A. **152:** 908 (July 4), 1953.

Report is made on a case of mediastinal lipoma because by its location and shape, it so closely simulated cardiac enlargement. The authors discuss the characteristic roentgenographic evidence, the possibility of sarcomatous changes in lipomas in the chest, and the necessity for surgical exploration. It is hoped that this report will cause such tumors to be considered in the diagnostic approach to enlargement of the cardiac silhouette which is otherwise unexplained.

KITCHELL

**Goodwin, J. F.: Fatality following Cardiac Catheterization Injury.** Brit. Heart J. **15:** 330 (July), 1953.

A fatality is reported following catheterization of a man 44 years old with calcareous mitral and aortic stenosis. A few minutes after the catheter slipped back from the pulmonary artery into the ventricle, the patient became pale, vomited and his pressure fell. After 12 hours, his pressure rose, but he remained severely ill. The electrocardiogram showed changes consistent with pericarditis. The blood potassium was elevated. He died within 40 hours of catheterization.

Necropsy showed a region of hemorrhagic discoloration in the epicardial fat over the right ventricle 5 cm. to the right of the descending left coronary artery.

The author suggests that the tip of the catheter be kept as far away from the lateral cardiac border as possible and that the patient should not be rotated with a catheter in place.

SOLOFF

**Greiner, T., and Gold, H.: Method for Therapeutic Evaluation of Diuretic Agents Administered Orally.** J.A.M.A. **152:** 1130 (July 18), 1953.

The first order of business in the treatment of the patient with congestive failure is to put to work an effective system of diuretic medication. The most satisfactory results have thus far been obtained with a maintenance regimen of injections of a mercurial diuretic. The problem of frequent injections over a period of years has stirred up interest in the development of agents that might be used by the oral route. Two of the problems presented by orally administered diuretics are similar to those of injected diuretics; that is, those of diuretic potency and systemic toxicity. Orally administered agents present a third problem of local gastro-intestinal irritation. Eight orally administered diuretic agents were examined for (1) their diuretic potency, and (2) the incidence of local gastrointestinal irritation. Diuretic potency was determined by comparing the response to various oral doses of diuretics with the response of the same patients to intramuscular injections of various doses of a standard injectible diuretic (Meralluride). Results showed there are marked differences between agents given orally when they are examined for their diuretic effectiveness in relation to the corresponding incidence of gastrointestinal irritation. In terms of the arbitrary expression of this relationship they ranged from ammonium chloride with a value of 52 up to one of the most recently developed compounds (Neohydrin), with a value of 284. No oral diuretic is free of unpleasant gastrointestinal side reactions and the range of utility is limited.

The average response to most of the orally administered materials are in the range that would be represented by 0.5 cc. of Meralluride intramuscularly.

KITCHELL

**Soloff, L. A., and Zatuchni, J.: Infectious Mononucleosis Associated with Symptoms of Acute Pericarditis.** J.A.M.A. **152:** 1530 (Aug. 15), 1953.

A case of infectious mononucleosis is reported in which the first symptoms were those of acute pericarditis. This case would suggest that the diagnosis of acute benign nonspecific or idiopathic pericarditis should be made only when all known causes of acute pericarditis have been excluded by history, physical examination and laboratory tests.

KITCHELL

**Neisen, E. H., Jr.: The Medical Aspects of Electric Shock Therapy (Including a Study of 192 Patients).** Am. J. M. Sc. **226:** 143 (Aug.), 1953.

A comprehensive review of the literature dealing with the medical aspects of electric shock therapy (EST) is presented together with the authors' experience with 210 series of electric shock treatments in 192 patients treated in a Veterans Hospital. Cardiovascular complications are the most important causes of death from electric shock therapy. The mechanisms whereby this therapy influences cardiac work and circulatory hemodynamics are analyzed. Electrocardiographic studies disclose the occurrence of many types of rhythm disturbances in association with electric shock therapy which are probably due to increased vagal tone and which can be abolished by the use of Atropine given 30 minutes before treatment. Patients with known heart disease can be prepared by salt restriction or the use of appropriate agents such as digitalis, diuretics, quinidine, or Pronestyl, depending upon specific indications. Few medical contraindications were found to electric shock therapy; these included myocardial infarction, aneurysm of the aorta, and uncompensated heart failure, acute infections and acute peripheral vascular disease. Curare may be useful in protecting the heart following the convulsive seizure. Electric shock therapy in the present series was found to be a safe method for treating psychiatric patients if reasonable precautions are taken in the selection and preparation of cases and if appropriate pretreatment medication is used.

SHUMAN

**Gziou, L. T., and Silverman, J. J.: A Bedside Method for Determining the Serum Chlorides as an Aid in Detecting the Chloride Depletion Syndrome in Patients Receiving Mercurial Diuretics.** Am. J. Med. Sc. **225:** 521 (May), 1953.

A bedside test for serum chloride measurement has been developed in order to detect hypochloremia in patients from whom a sample of urine is not readily available for urinary chloride measurement. In performing the test, one drop of 10 per cent potassium chromate solution is added to 10 drops of serum obtained from a specimen of clotted blood. Silver Nitrate, 0.73 per cent solution, is added dropwise until a reddish brown color is produced after gentle shaking. Each drop of silver nitrate represents 15 mg. of chloride, and the average normal patient requires 23 to 25 drops (345 mg. to 375 mg. of chloride). The results obtained in 127 determinations were compared to those in the same blood samples using the standard Schales and Schales procedure. There was less than 5 per cent variation in the results of both methods in 65 per cent of the specimens; the variation was above 15 per cent in 3.2 per cent of the specimens. Although the method is not precise, it is adequate to screen out states of severe hypochloremia and may be easily performed at home or in office practice.

SHUMAN

# BOOK REVIEWS

**Experimental Atherosclerosis.** *Louis N. Katz and Jeremiah Stamler.* American Lectures Series in Metabolism, No. 124. Springfield, Ill., Charles C. Thomas, 1953. 375 pages, 84 tables, 37 figures, 7 color plates. $10.50.

This monograph is very timely indeed, for today atherosclerosis has the distinction of being Public Killer Number One. And, if the present public health standards continue as they surely will, atherosclerosis will have this distinction for many years to come. Running through this monograph, one senses the justified impatience and intolerance which the authors feel toward the prevailing pessimistic attitude that atherosclerosis is progressive, incurable and a dire consequence of living. The culmination of this impatience, paced by a note of optimism, is shown on page 274 where the authors clearly point out that there is tentative experimental evidence which indicates that this disease may be reversible.

The scope of this monograph embraces almost the whole spectrum of atherosclerosis. The authors have a fine discussion of geographical medicine with especial reference to atherosclerosis. Evidence is assembled which is strongly suggestive, but not conclusive, on the bearing of dietary and nutritional factors in atherosclerosis. This evidence is based on an evaluation of dietary habits and degree of atherosclerosis in such populations as Kirghiz Plainsmen, Eskimos, Ceylonese and Chinese. The section on human clinicopathologic evidence which is based upon a study of diseased states in which disturbed cholesterol metabolism is involved, is well presented. In this section, in a future edition, it may be well to analyze critically the differential incidence of atherosclerosis in women as compared with men in the various diseased states. (The important difference in sex distribution is considered on page 256 of their monograph in great detail but from another viewpoint.) Included in this section are the controversial subjects of undernutrition and overnutrition, high fat and low fat diets, hypocholesterolemia and hypercholesterolemia. Again, the authors do not draw any definite conclusions. In this chapter as in all other chapters the authors proceed to summarize the pertinent literature on any controversial subject and then evaluate the evidence and reinterpret the data in terms of modern concepts. To add to this Herculean task, they often point out critical experiments or studies which would help to clarify the points in question.

Chapter 3, which collates the evidence from a biochemical viewpoint, gives a lucid picture of the advances made in this field during the past five years. Included in this section is a discussion of alpha and beta lipoproteins, Gofman molecules and other cholesterol entities. The discussion of the significance of the total cholesterol-lipid phosphorus ratio as an index of atherogenesis is well done although certain of the statements concerning the inconsistencies in the hypothesis and in certain statistical concepts (pages 94 and 95) are open to question. A discussion of cholesterol turnover rates and biosynthesis of cholesterol as studied with labelled precursors would be a worthwhile addition to this section.

Since the early days of experimental atherosclerosis many theories have been put forth both as to etiology and as to curative agents. In chapter 4, Experimental Atherosclerosis, which is by far the largest chapter in the monograph, the authors truly demonstrate the wide scope of their studies. In this chapter the many rumors and empiric findings which abound in the field of atherosclerosis are subjected to strict scientific disciplines. Accordingly, such basic issues as sex, age, nutritional state, disease processes, hormonal imbalances and dietary factors are studied and presented with unusual skill and organization.

This monograph will be useful to many individuals. Students, members of the House Staff and practitioners will covet it, for there is a clear, concise statement of the problem as it stands today. The excellent bibliography is arranged so that, with a modicum of effort, it will enable the reader to acquire knowledge of the disease from an introductory level to an advanced degree. For the investigators the authors provide an authorative summary of the problem and a mature and far-reaching philosophy toward this disease. This, coupled with the fine presentation of the further facets of research required, should prove to be most helpful and instructive.

MENARD M. GERTLER

**Clinical Disorders of the Heart Beat.** *Samuel Bellet, M.D.* Philadelphia, Lea & Febiger, 1953. 373 pages, 164 figures, 3 tables. $8.50.

Early in this century, interest in disorders of the heart beat was at its height, and textbooks of medicine devoted considerable space to the cardiac arrhythmias. A series of monographs appeared on the subject, foremost among which are the publications of Sir Thomas Lewis. Interest in the topic then slackened, and in the following decades, the arrhythmias received bare mention in the then current texts. The appearance of Myron Prinzmetal's publication, *The Auricular Arrhythmias*, in 1952, indicated an awakened interest in the arrythmias, which are today the center of growing controversy.

Samuel Bellet's timely textbook is admirably suited to the interest and needs of the general prac-

titioner, the internist, the surgeon, the anesthesiologist and the cardiologist alike. The book is in four sections. Included in the first section are detailed delineations of cardiac neuroanatomy and physiology, a lucid classification of the arrhythmias, and—as guides to diagnosis—thorough descriptions of clinical manifestations. In the second section, each of the arrhythmias is discussed individually, from etiologic considerations through clinical management.

The third section is all too brief. In this important section, clinical states in which the arrhythmias occur are described clearly and concisely. The correlation of the diseased state with the occurrence of the arrhythmias is stressed. A detailed discussion of the action and usage of digitalis, quinidine, and procaine amide in the management of disorders of the heart beat comprises the fourth and final section.

Unfortunately, the neurosurgical approach to the management of disorders of the heart beat receives very little discussion; inclusion of an evaluation of this approach in later editions would be valuable.

The illustrations are clear, and the legends are most helpful. The author is to be congratulated on the clarity and comprehensiveness of the text, and on the format, which commend this book to all segments of the profession.

GEORGE C. GRIFFITH

# BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

**Leistungssteigerung. Leistung, Übermudung, Gesunderhaltung.** *Prof. Dr. Max Hochrein and Doz. Dr. Irene Hochrein-Schleicher.* Stuttgart, George Thieme Verlag, 1953. 283 pages, 53 figures, 20 tables. DM27.

**Salt and The Heart.** *E. T. Yorke, M.D., Attending Cardiologist, Alexian Brothers Hospital; Associate Cardiologist, St. Elizabeth Hospital; Dispensary Physician, Elizabeth General Hospital, Elizabeth; Consultant in Medicine, Rahway, N. J.* Linden, N. J., Drapkin Books, 1953. 83 pages, 4 figures. $3.45.

**Gourmet Cooking for Cardiac Diets.** *Florence Field. Introduction by Harold Feil, M.D.* Cleveland and New York, World Publishing Company, 1953. 350 pages. $3.50.

**Electrical Methods of Blood-Pressure Recording.** American Lectures in Medical Physics #155. *Frank W. Noble, M.E.E. National Heart Institute, National Institutes of Health, Public Health Service, Federal Security Agency, Bethesda, Md.* Springfield, Ill., Charles C Thomas, 1953. 56 pages, 12 figures, $3.00.

**The Hypertensive Disorders of Pregnancy.** American Lectures in Circulation #188. *Ernest W. Page, M.D. Associate Professor of Obstetrics and Gynecology, University of California, School of Medicine, San Francisco, Calif.* Springfield, Ill.. Charles C Thomas, 1953. 120 pages, 2 figures, 5 tables. $3.75.

**Das Elektrische Herzbild. Die Grundlagen Eines Neuen Elektrokardiographischen Verfahrens.** *Dr. Ing. Hibil, Wilhelm Ernsthausen.* Munchen, Germany, Verlage Fur Brophysik, Hermann Rinn, 1953. 231 pages, 227 figures, 12 tables. DM48.

# AMERICAN HEART ASSOCIATION, INC.

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## SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

Applications for membership in the Congress, scheduled to convene in Washington, D. C. September 12 through 17, 1954, will continue to be received indefinitely. A booklet containing a membership application form and detailed information concerning the Congress is available from the Secretary-General, L. W. Gorham, M.D., at 44 East 23rd Street, New York 10. It is suggested that all those interested in attending the Congress submit their applications at the earliest possible date to facilitate arrangements for hotel accommodations and attendance at social functions.

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although it has been customary in previous years to waive registration fees for professional members of the American Heart Association attending the annual Scientific Sessions, the heavy expenses entailed by the enlarged and integrated sessions of the forthcoming Congress and the many events associated with an international meeting of this kind require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events planned for Congress delegates, the exhibits and special sightseeing tours to medical installations in Washington and its environs. Also included are the printed program, directory of registrants, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns and nurses.

The Congress will convene with opening ceremonies in Constitution Hall on Sunday, September 12. Scientific sessions and exhibits at the National Guard Armory are scheduled for the next five days.

At the conclusion of the Congress, there will be a series of tours to other medical centers in the United States and Canada.

## SECTION ON CIRCULATION

The Section on Circulation of the Scientific Council is planning a special scientific session for members on matters of peripheral circulation as well as a general session to be held in connection with the Second World Congress of Cardiology in Washington, D. C., September 12–17. The exact dates of this Section's meeting will be announced later.

The Executive Committee of the Section on Circulation will meet on Monday evening, September 13. The Annual Dinner of the Section will be held on Wednesday evening, September 15, at the Shoreham Hotel. Additional details may be obtained from the Secretary, Grace M. Roth, Ph.D., Mayo Clinic, Rochester, Minn.

## COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

A half-day program devoted to a discussion of rheumatic fever will be presented at the Annual Meeting of the American Rheumatism Association at the St. Francis Hotel, in San Francisco, on Friday and Saturday, June 18, and 19. The program will be presented by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association in cooperation with the American Rheumatism Association.

## COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

The Annual Meeting of the Association's Council for High Blood Pressure Research will be held in the fall this year instead of the spring as has been the custom. The meeting has been scheduled for Friday and Saturday, October 22 and 23, in Cleveland. The subject

of the scientific program will be "The Metabolism of Muscles and Nerves as it Relates to High Blood Pressure." Irving S. Wright, M.D., New York, Past President of the Association, is Chairman of the Program Committee. A program for the general public will feature a discussion on problems of retirement.

The Proceedings of the 1953 Annual Meeting of the Council for High Blood Pressure Research have been published and are available from the American Heart Association or local Heart Associations. The volume, which costs $2.00, includes five reviews of recent original investigative work presented at the 1953 Annual Meeting of the Council held in Cleveland last May. The authors are R. W. Sevey, Georges M. C. Masson, Simon Rodbard, D. M. Green and George A. Perera. The subjects covered include the relations between hypertension and the anterior pituitary, the adrenal cortex, renin, salt-water balance, sodium metabolism and electrolyte metabolism.

The Proceedings of the 1952 meeting is still available at a cost of $1.75, paper-bound.

## COUNCIL ON COMMUNITY SERVICE AND EDUCATION

The following have been named as officers and members of the Executive Committee of the Association's Council on Community Service and Education:

*Chairman:* Martin Cherkasky, M.D., Director, Montefiore Hospital, New York.

*Vice Chairman:* William A. Brumfield, Jr., M.D., Chairman, Department of Preventive Medicine and Public Health, New York State University College of Medicine, Syracuse.

*Members-at-Large:* Mrs. Bess Dana, Director, Social Service Department, Beth Israel Hospital, Boston; Mrs. Myrtle H. Coe, School of Nursing, University of Minnesota; Hugh McCulloch, M.D. Chief of Staff, La Rabida Jackson Park Sanitarium, Chicago.

*Committee Chairmen:*

*Committee on Education:* George N. Aagaard, M.D., Dean, Southwestern Medical School, University of Texas.

*Committee on Rehabilitation:* E. A. Irvin, M.D., Medical Director, Cadillac Motor Car Division, General Motors Corporation, Detroit.

*Committee on Volunteers:* Mrs. Douglass O. Burnham, Watertown, Conn., National Chairman, American Heart Association's Committee on Volunteer Activities.

*Research Study Committee:* Ancel Keys, Ph.D., Director, Laboratory of Physiological Hygiene, University of Minnesota.

*Nutrition Committee:* Herbert Pollack, M.D., New York, Consultant in Nutrition to Surgeon General, U. S. Army.

*Committee on Community Programs:* Ray E. Trussell, M.D., Director, Hunterdon Medical Center, Flemington, N. J.

*Program Committee:* Harold Feil, M.D., Past President, Cleveland Area Heart Society.

*Ex officio members:* President, President-Elect of the American Heart Association, Chairman of Scientific Council, Chairman of Council on Rheumatic Fever and Congenital Heart Disease.

## AMERICAN HEART ASSOCIATION PANELS AT AMERICAN MEDICAL ASSOCIATION MEETING

The American Heart Association is planning a four-day series of one-hour panel discussions on various aspects of cardiovascular disease at the 103rd Annual Meeting of the American Medical Association, to be held at the Civic Auditorium in San Francisco from June 21–25. The program is being arranged by Dr. Howard B. Lewis, University of Oregon School of Medicine.

Dr. J. Scott Butterworth's fluorodemonstrator exhibit, which was awarded a gold medal at last year's meeting of the American Medical Association in New York, also will be presented at this year's meeting. The exhibit features the Association's rubber heart models illustrating various disease conditions. It is expected that there will be an exhibit of other educational materials available from the Association.

## ANNUAL REPORT

The Association's 1953 Annual Report, "The Heart Story," has been published. Copies are available on request.

## AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

The deadline for the submission of abstracts of papers for presentation at the Annual Meeting of the American Society for the Study of Arteriosclerosis to the Program Chairman is May 31. The meeting will be held at the Sheraton Hotel in Chicago on October 31 through

November 1, 1954. Program Chairman is Arthur C. Corcoran, M.D., Cleveland Clinic, Cleveland, Ohio.

## VERMONT SEMINAR

A seminar on Cardiac Arrhythmias, sponsored by the Vermont Heart Association, and the University of Vermont College of Medicine, will be held in Burlington, Vermont, on Thursday and Friday, September 9 and 10, 1954. It will be conducted by E. Lepeschkin, M.D., with D. Scherf, M.D., and S. Bellet, M.D., as guest speakers. Participants are urged to bring difficult cases for discussion. Participants not connected with the University of Vermont will be charged $10.00 to cover expenses. Further information can be obtained from Dr. Lepeschkin, University of Vermont College of Medicine, Burlington, Vt.

On September 11, 1954, a Symposium on the U wave of the Electrocardiogram will be held in Burlington under the same joint sponsorship. It will be conducted by Dr. Lepeschkin. Drs. C. Papp, M. Segers, J. H. Palmer and H. Hecht expect to participate. Those interested in presenting papers of no more than 15 minutes' duration are invited to submit the title to Dr. Lepeschkin. It is planned to publish the proceedings of the Symposium.

## CHAIR OF CARDIOVASCULAR RESEARCH

Dr. Thomas Findley, head of the section of internal medicine at New Orleans' Ochsner Clinic, will fill the Chair of Cardiovascular Research at the Medical College of Georgia in Augusta. The Chair was recently established through a grant made by the Georgia Heart Association. He will also serve as Director of the Georgia Heart Association Laboratory of Cardiovascular Research at the Medical College. A similar Chair of Heart Research will be established at the Emory University School of Medicine in Atlanta.

## MEETINGS

April 26–May 2: International Congress of International College of Surgeons; Sao Paulo, Brazil; Dr. Max Thorek, Secretary-General, 1516 Lake Shore Drive, Chicago, Ill.

April 27: Annual Spring Scientific Session, New York Heart Association; New York Academy of Medicine, 2 East 103rd Street, New York, N. Y.

May 5–8: Fourth National Conference on Health in Colleges; Hotel Statler, New York. Charlotte V. Leach, Secretary, 1790 Broadway, New York.

June 14–18: Canadian Medical Association; Vancouver, B.C. T. C. Routley, M.D., General Secretary, 244 St. George St., Toronto 5, Ont.

June 18–19: American Rheumatism Association; San Francisco; W. H. Kammerer, Secretary, 33 East 61st Street, New York 21, N. Y.

June 19: International Society of Angiology, North American Chapter; Hotel Mark Hopkins, San Francisco, Calif. Dr. Henry Haimovici, Secretary, 105 East 90th Street, New York, N. Y.

June 20: Society for Vascular Surgery; San Francisco; George D. Lilly, Secretary, 25 S. E. Second Ave., Miami 32, Fla.

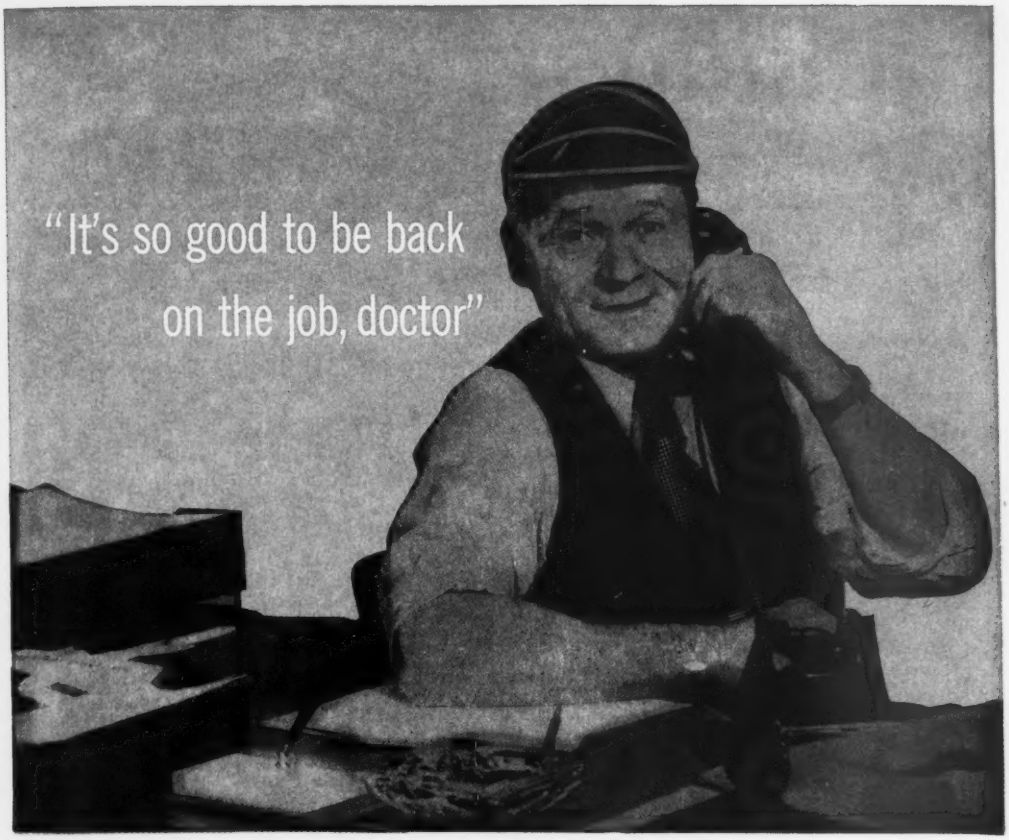
June 21–25: American Medical Association, Annual Meeting; San Francisco; Dr. George F. Lull, Secretary, 535 North Dearborn Street, Chicago 10, Ill.

July: South American Congress of Angiology; Sao Paulo, Brazil; Dr. Rubens Carlos Mayall, Rua Senador Vergueiro 73, Rio de Janeiro, Brazil.

July 9–10: European Society of Cardiovascular Surgery; Edinburgh, Scotland; A. J. Slessor, Department of Surgery, University New Building, Edinburgh 8, Scotland.

July 20–24: International Conference on Thrombosis and Embolism; Basle, Switzerland; W. Merz, M.D., Honorary Secretary, Chief Medical Officer, Gynecological Clinic, University of Basle, Basle, Switzerland.

August 9–13: National Medical Association; Washington, D. C. John T. Givens, Secretary, 1108 Church Street, Norfolk 10, Va.

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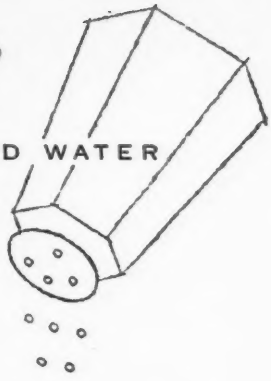

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